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ANDROGEN CONTROL IN CARCINOMA OF THE PROSTATE*

JOHN P. BOWLER, M.D.,† AND SCOTT F. PEDLEY, M.D.‡

HANOVER, NEW HAMPSHIRE

THIS paper presents a brief report of the early results of castration in 22 cases of carcinoma of the prostate seen during 1942. The physiologic rationale of castration has perhaps been the outstanding item in recent urologic literature, much of which has been controversial and contradictory. With the understanding that many details of the present concept are missing, some not proved and others doubtless later to be changed or disproved, the present basis of attack will be briefly outlined.

Dr. Charles Mayo has been quoted as having made the statement many years ago, "No matter what you do for carcinoma of the prostate, you do the wrong thing." The persistence of this pessimistic attitude has not been without a basis in the poor results generally achieved. Until recently, transurethral resection for the relief of obstruction and radiation for the relief of pain have contributed considerable alleviation, temporary, to be sure, to these patients. The position of the advocates of radical perineal prostatectomy as the only possible direct attack on carcinoma of the prostate is surgically sound, but it fails to meet the general problem, for many reasons. First, the disease originates most frequently in the posterior lamella, thereby giving rise to urinary symptoms relatively late in its development; second, the carcinoma is slow growing and is well advanced by the time that the typical patient of prostatic age, expecting as he does a certain degree of urinary difficulty, decides to obtain medical advice. The most enthusiastic supporters of radical perineal prostatectomy agree that the percentage of cases to which it can be applied — namely, those in which a malignant lesion is still confined within the prostate capsule when the patient is first seen — is not over 5 per cent. At least 95 per cent of prostatic carcinomas must therefore be treated by other methods. The importance of the lesion is brought out by the fact that the number of men living into the prostatic age — that beyond sixty-five — doubled in the United States between 1911 and 1935.[1]

Beginning in 1933, Dmochowski,[2] Kutscher and Wolbergs,[3] the Gutmans[4] and other workers investigating the sources of acid phosphatase in urine discovered that normal human prostate tissue is extremely rich in this material. Acid phosphatase is an enzyme, a constituent of many tissues of the body, but, as noted by these writers and others, it is present in far greater concentration in the adult prostate gland and prostatic fluid than in any other part of the body. Significant is the fact that it occurs in extremely low concentrations in the prepubescent prostate. Most carcinomatous prostate tissue contains large amounts of acid phosphatase, whereas highly malignant tumors, being made up of functionally immature cells, contain but little of it. When metastasis of a prostatic carcinoma occurs, presumably the acid phosphatase is allowed to escape into the blood and lymph and the blood-serum level is elevated. The acid phosphatase is measured in units per 100 cc. of serum, 3 to 5 units being regarded as the range of normal by various workers. Elevated levels may fail to appear because of insufficient invasion, lack of differentiation of the tumor or preceding treatments, as will be discussed later.

Serum alkaline phosphatase is likewise an enzyme, but is less specific than acid phosphatase regarding its prostatic origin. It is elaborated at sites of osteoblastic activity, particularly bony metastases where new bone is being formed. Therefore, Paget's disease and other lesions characterized by osteosclerosis must be excluded if one employs the level of this substance as a measure of osteoblastic metastatic lesions.

It can be inferred, then, that elevation of serum acid phosphatase signifies prostatic-cell activity communicable to the blood stream, therefore of extracapsular prostatic tissue and therefore presumably of carcinoma. Likewise, elevation of the

*From the Urological Service, Hitchcock Clinic, Hanover, New Hampshire.

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†Dean, Dartmouth Medical School; surgeon, Mary Hitchcock Memorial Hospital.

‡Staff assistant, Mary Hitchcock Memorial Hospital.

serum alkaline phosphatase accompanies the change in the metastatic bone lesion from one of osteolytic to one of osteoblastic type, thus indicating sclerosis and regression as a result of a defensive reaction of bone to the tumor.

The findings of Sullivan[5] and the Gutmans[6] (Table 1) illustrate clearly the incidence of elevated values in carcinoma of the prostate in the presence of metastases. In a series of 200 cases of prostatic carcinoma, 85 per cent of 130 cases with demonstrable bone metastases showed an elevated acid serum phosphatase. Seventy cases without metastases as shown by x-ray examination showed slight elevation in 11 per cent. Glands with benign hypertrophy or prostatitis and normal glands showed no elevation, whereas of 570 cases of nonprostatic disease ten per cent showed elevation, demonstrating extraprostatic origin of acid phosphatase. It is thus evident that the serum acid phosphatase is not elevated in cases of prostatic carcinoma confined to the capsule of the gland. Unfortunately, therefore, such elevation is not corroborative evidence of the nature of the lesion prior to metastatic or extracapsular involvement.

TABLE 1. *Acid Serum Phosphatase Levels in Various Prostatic Conditions (adapted from Sullivan[5] and Gutman and Gutman[6]).*

CONDITION	NO. OF CASES	PERCENTAGES OF CASES WITH VARIOUS LEVELS (UNITS) OF ACID SERUM PHOSPHATASE					
		3.0 OR LESS	3.0—4.9	5.0—9.9	10—99	100—999	1000 OR OVER
Prostatic carcinoma:							
Bone metastases (x-ray)	130	15	12	25	35	9	4
No bone metastases (x-ray)	70	89	11				
Prostatic hypertrophy	75	100					
Prostatitis	10	100					
Nonprostatic disease	570	90	8	2			
Normal	30	100					

The first investigators to recognize the implications of the results of this experimental research were Huggins and his associates,[7-9] who at that time had gone back, so to speak, to investigate the effect of castration or administration of estrogens on prostatic hypertrophy in dogs. On the basis of this work, they published in 1941 an outline of androgen control of prostatic tissue by surgical castration. They reported several cases of metastatic prostate carcinoma subjected to castration in which there was a sharp postoperative reduction in serum acid phosphatase and a rise in serum alkaline phosphatase followed by a gradual decline, and in which these chemical changes were accompanied by marked clinical improvement.

In summary, the rationale of the present approach is the removal of stimulation of the prostate cells by androgen. This is being effected by surgical castration, irradiation castration, neutralization with administration of estrogens and combinations of these methods (Fig. 1).

As shown, surgical castration removed the source of androgen, whereas estrogen may be administered as its neutralizer. In other words, the adult prostatic epithelium is activated by the androgenic gonadotropic hormone, resulting in an increase of the tumor, in an elevated serum acid phosphatase and in the production of symptoms. Castration removes the source of androgen and inactivates the prostatic epithelium, the tumor decreases, the acid phosphatase decreases, and the symptoms decrease. The effect of androgen is similarly neutralized by the use of estrogen.

The use of estrogen as the sole therapeutic program has been reported by Herbst[10] and others as having favorable results, both symptomatically and regarding changes in the gland itself. We have not used it in any case as the sole procedure, but have reserved it for the treatment of delayed recurrences following orchidectomy, with at least temporary beneficial results in several cases.

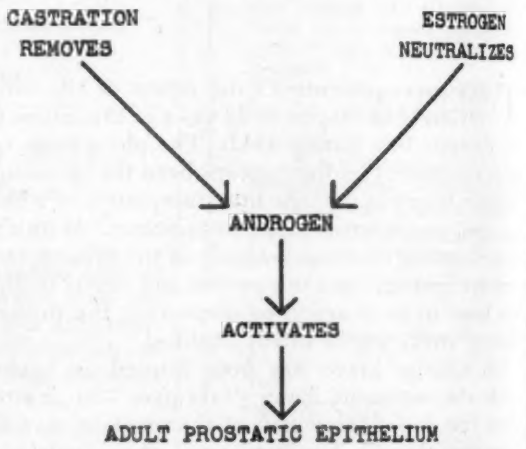

FIGURE 1. *Mode of Action of Castration and Estrogen Therapy.*

Irradiation castration has been applied for some years by Munger,[11] who seems to think that the results are quite comparable with those of surgical castration. It is highly probable that irradiation castration has in the past been unwittingly accomplished by inclusion of the scrotal field in deep-therapy exposures.

In every case of the present series a surgical castration was done, at times in conjunction with radiation and administration of estrogen in cases in a hopelessly advanced stage. The usual complete castration was performed in the early cases of the series, but in the great majority a subcapsular orchidectomy was done after the manner described by Chute[12] in 1942. Figure 2 demonstrates the procedure. Through separate lineal scrotal incisions, the testicle is delivered from the scrotum. The tunica albuginea is then incised longitudinally opposite the epididymis, and the entire rete testis is removed en masse by instrumental and finger curetting. After ligation of the intracapsular blood supply of the rete, the capsule is closed with a locked suture, the tissues are restored to the scrotum, the skin incisions are

closed, and a suspensory dressing is applied. The capsule of the testis usually fills with blood, which becomes organized, and there is but little change in the palpable or visible contents of the scrotum. The latter advantage appears to be of some importance in the introspective processes of the patient. In this connection it is of interest that we have yet to encounter refusal of this procedure by any patient.

All the cases in this series were those of adenocarcinoma of the prostate gland, proved either by demonstrable metastatic bone lesions or by pathological examination of removed tissue. The average age of the patients was seventy years, ranging from fifty-four to eighty-six years. Dysuria was present in 17 cases, an appreciable residual urine in 10, and complete urinary obstruction in 4. An orchidectomy was carried out as the sole procedure in 4 cases; it was done following transurethral resection in 15 cases, and at varying intervals following transurethral resection or prostatectomy elsewhere in 3 cases. The patients in the first group received no x-ray therapy, 3 of the second group received it either previously or combined with the orchidectomy because of the advanced stage of disease, and all 3 patients in the third group at the time of operation had received deep x-ray therapy from one to two years previously.

Bone metastasis was demonstrable by x-ray examination in 10 cases, but in only 6 of these was pain given as a symptom. Thus, 4 cases without pain showed bone involvement, whereas in 4 with pain no metastatic extension could be shown. This observation seemed to contradict an old concept that pain in the back, lumbar region or buttocks is complete corroborative evidence of extension of a physically diagnosable malignant prostate. This concept probably still holds true, but the point to which it leads is that a negative x-ray examination of the lumbar spine and pelvis, like all negative findings, does not justify exclusion of bone metastasis.

This point was forcibly demonstrated by a sixty-seven-year-old patient who had received transurethral resection and deep x-ray therapy elsewhere. The preliminary x-ray films were negative. Two and a half months following the performance of orchidectomy there was extensive osteosclerosis of the third lumbar vertebra and sharply defined areas were seen in both iliums. On review of the preoperative

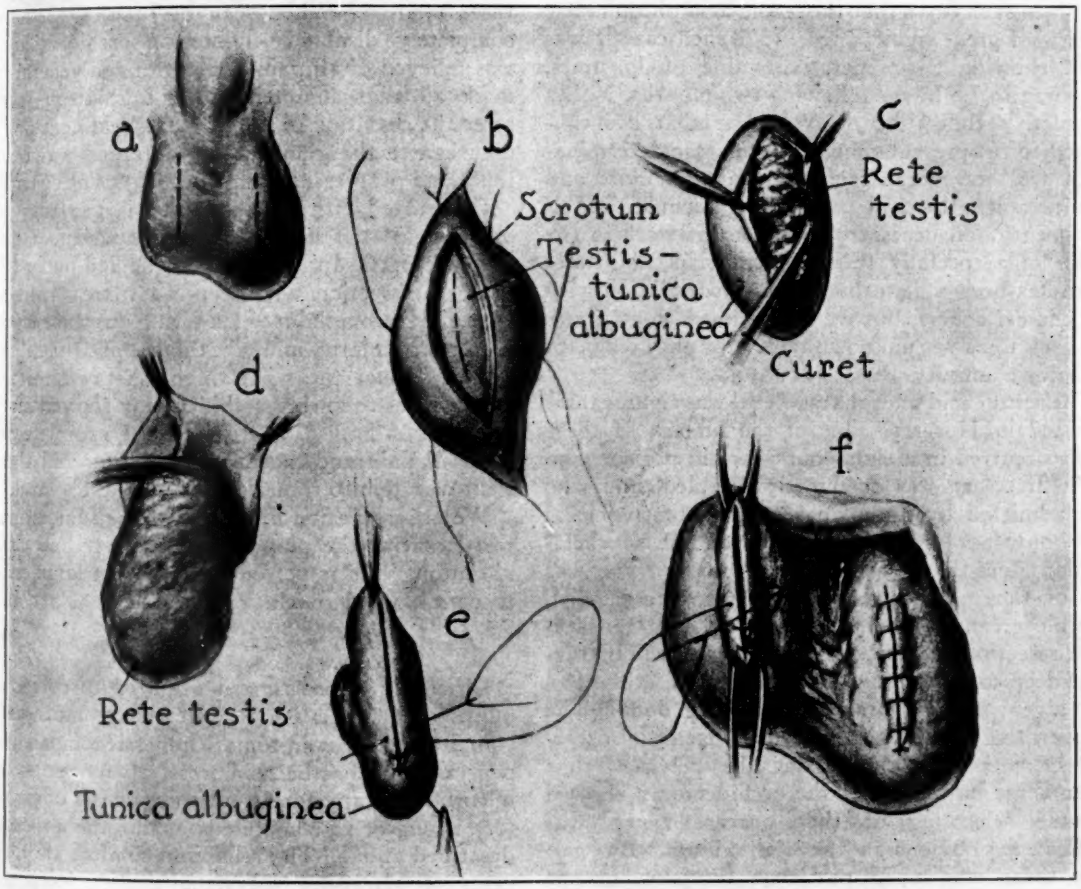

FIGURE 2. *Operative Steps in Castration.*

films by the X-ray Department, fine variations in density could be demonstrated at the sites of these later obvious metastases.

In another case of obvious clinical carcinoma of the prostate, a preoperative bone roentgenogram was definitely negative. Rectal examination revealed characteristic induration and irregularity of the gland. The clinical response of cessation of urinary symptoms was most marked and remained so. On postoperative check-up three months following orchidectomy, roentgenograms showed obvious bone involvement in the right ilium and symphysis.

It is in such cases that the serum acid phosphatase level is of great significance. In 1 such case it was high, showing a preoperative value of 15 units, dropping to 7.8 in the following two months, with a complete stabilization of symptoms that has continued to the present time. Phosphatase determinations are, however, affected by many factors and require a lengthy and painstaking technic, and it has been found necessary to leave this work in the hands of a specially trained technician. At times there has been a disturbing lack of correlation with the clinical course, but we are inclined to attribute this lack to as yet unknown factors of physiologic or pathologic activity.

The serum acid phosphatase level was significantly elevated in 14 cases. One of the highest of these levels occurred in a sixty-four-year-old patient who when first seen was completely disabled, and who was admitted by ambulance, with extensive local and bony involvement and enlarged left supraclavicular nodes that were positive on biopsy. This was one of the most extreme cases encountered. All possible means of therapy were used. A transurethral resection was done because of marked obstruction, deep x-ray therapy was indicated, stilbestrol was given, and an orchidectomy was done. The preoperative x-ray film showed extensive osteoblastic metastases throughout the pelvis. Films taken three months after the orchidectomy showed extreme sclerosing of these areas, which was particularly obvious in the right ilium. By that time there was a 75 per cent recession in the supraclavicular nodes, and the general clinical result was dramatic. This improvement continued for seven months and the patient returned to overseeing his farm. At the end of eight months of normal health, extension and pain recurred, and a rapid progression to a general carcinomatosis followed. This late failure was in contradiction to what was to be expected from the initial clinical picture.

Recalcification of bone following orchidectomy is exemplified in a patient of seventy-seven presenting marked dysuria and bladder irritability, with extensive destruction of the left pubis. Following orchidectomy alone there was almost immediate complete relief of the bladder symptoms, and within a few months there was a dense, smooth and complete reconstruction of the pubis, with relief of pain on walking. This improvement has now continued for one year. The patient was one of the 4 on whom orchidectomy only was done, and it is of interest that the results in this small group, as yet unexplained, are uniformly excellent to date.

Response to orchidectomy following relapse after x-ray therapy is illustrated by a fifty-four-year-old patient who was first seen in November, 1941, with obstruction and bony metastasis. Following resection and an intensive course of deep x-ray therapy, which included x-ray castration, he was relieved for three months. When seen in June, 1942, he was completely disabled. Following orchidectomy he was relieved of all pain and performed general farm work all that summer and fall. Sixteen months after the cessation of the original treatment and ten months after the orchidectomy, he returned with recurrence and progression, which could not be controlled.

Contrasted with the above case is a seventy-year-old patient who had a similar management before orchidectomy. In March, 1941, he had had a transurethral resection and deep x-ray treatment elsewhere. His complaint when seen by us was recurrent pain, particularly in both thighs, and inability to flex or adduct the right thigh. X-ray films taken two months following orchidectomy showed marked sclerosis of bone. There followed complete relief from all pain and muscular disability, and the patient was able to return to the care of his farm.

We are interested in grading these tumors in correlation with the phosphatase activity and clinical variations, but as yet our series is not large enough to permit valid conclusions.

* * *

Obviously, more time is required to corroborate our present observations, but the promptness and completeness of symptomatic relief as compared with past methods has been impressive. As yet no other means of therapy for far-advanced cases offers relief for so long or so completely as do the procedures described above. The relief and comfort afforded in cases of remission following routine deep x-ray therapy have been striking. Many carcinomas of the prostate are of low grade and many patients with such tumors live for long periods, and it is much too early to judge the long-time effectiveness of these procedures. On the other hand, these cases present the first tumors available to the clinician in large numbers in which the question arises whether cancer is the result merely of an intrinsic urge of a cell to grow, or the result of a stimulation by substances that may be brought under therapeutic control.

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Discussion

Dr. Richard W. Robinson, Laconia: There is little doubt that some of the most dramatic recent occurrences in surgery, from the symptomatic point of view, result from castration in advanced cases of carcinoma of the prostate. It appears from the literature that quite comparable results can be accomplished by the neutralization of these androgens through the constant and sufficient use of neutralizing estrogen. We should not, however, lose sight of the fact that even in view of the quick relief these patients get from their symptoms, the problem of carcinoma of the prostate is not solved by procedures of this kind.

Some months ago Randall reported the end results in 5 cases observed over a period of eight years in which castration had been done for carcinoma of the prostate, and in which there were no cures, all the patients eventually dying of carcinoma. I believe that other similar results have been published, and I have recently heard presented facts that indicated that after a period of a year and a half to five years, the carcinoma progresses in the usual manner or even sometimes in an apparently accelerated one. This being so, one should certainly attempt to make a diagnosis of carcinoma in the hope of surgical cure.

Although carcinoma of the prostate, because of its location in the posterior lobe of the gland, does not manifest itself early by urinary symptoms, a yearly rectal examination of patients over the age of forty-five would reveal a great number of carcinomas that would otherwise remain undiagnosed until it was too late even to consider a radical total removal of the prostate such as Young advocates.

One of the most interesting questions is why dramatic and quick relief is obtained not only from the pain but also and particularly from the obstructive effects of these large carcinomas. It does not seem possible that within the course of a week or ten days, as so often happens, any change in the cellular structure or any regression of a carcinomatous mass could possibly take place. I wonder whether the explanation might not be that some change occurs in the vascular supply of the carcinomatous mass. Perhaps Dr. Bowler or Dr. Pedley can enlighten us on this phase of the subject.

Another interesting point is that there is more than one type of carcinoma of the prostate. Certain types, particularly the small-celled, rapidly growing, malignant one, do not yield to the removal of androgens as do the majority of these growths. It will be interesting to find out whether carcinomas actually developed in the hypertrophied mass of an adenomatous prostate yield to the removal of androgens in the same way as does carcinoma of the true prostate. There is considerable doubt whether the benign adenoma that develops a carcinoma in the center of it is of true prostatic origin.

Dr. Isadore J. Zimmerman, Manchester: Dr. Bowler and Dr. Pedley have made a valuable contribution to this meeting by reviewing the recent work on hormonal control in carcinoma of the prostate and by recounting their experiences during the past year. The discovery of the relation between the androgens and carcinoma of the prostate will always rank as an important milestone along the hard road toward the solution of this vexing problem.

My own experience with the use of castration and of stilbestrol has closely paralleled that of Dr. Bowler and Dr. Pedley. Clinical improvement is frequently apparent in a matter of days. Objectively the prostate becomes smaller and softer, but usually remains fixed and takes on a peculiar consistence that must be palpated to be appreciated. Histologically there is actual degeneration of carcinomatous cells.

The effect of stilbestrol on the testis is of some interest in evaluating the mechanism of its eventual effect on prostatic carcinoma, in addition to its neutralizing effect on the androgens. With the co-operation of our pathologist, Dr. Robert Biron, I have been able to show that the administration of stilbestrol results in changes in the testicle resembling those found following irradiation.

Like Dr. Bowler and Dr. Pedley, I have not been willing to rely on stilbestrol alone but have given it following castration, hoping in this way to neutralize any androgens that might be elaborated outside the testis, perhaps in the adrenal glands.

The subcapsular orchidectomy reviewed this morning is simple to perform, is not disabling, and leaves the patient with a reasonably ornamental facsimile. I have found it perfectly easy to do both subcapsular orchidectomies through a single, small, linear scrotal incision.

I might say a word about the effect of regression in the size of the tumor following orchidectomy. The sphincter musculature of the bladder is involved in varying degrees by the carcinoma. Further regression of the tumor with orchidectomy following resection occasionally results in incontinence. It has been my practice, therefore, where feasible, first to castrate the patient, and after the maximum amount of regression has occurred to decide whether tissue ought to be removed, and if so how much of it.

It is obvious that, as has been pointed out today, in the short period of two years it is impossible truly to evaluate the long-range significance of castration. To the great majority of these patients, castration or stilbestrol or both unquestionably bring relief from symptoms and regression of the carcinoma and even of the metastatic lesions. It is, therefore, with no intent to detract from the true value of this work and from the gratifying immediate results obtained in the vast majority of the patients that I re-emphasize what Dr. Bowler and Dr. Pedley have demonstrated in 2 of the cases reported. I refer to the universal experience of seeing with dismay the occasional resumption of the growth of the tumor after a period of latency, and also out-and-out failures. We must, therefore, temper our enthusiasm with the facts in so far as we know them, as Dr. Bowler and Dr. Pedley have carefully done in evaluating this work. Further, we must continue to be on the alert for early cases of carcinoma of the prostate by doing a rectal examination routinely on every male patient over forty-five years of age.

Dr. Bowler (closing): There is little that need be added. It is obvious that one has to be extremely guarded to avoid overenthusiasm. On the other hand, the subject is of great interest in connection with any biologic conception of malignancy, in that this is the first tumor occurring commonly in clinical practice in which one can observe and speculate on the relation of malignancy to glandular secretions.

There is no answer at the present time to Dr. Robinson's question about the mechanism of the relief that these patients get from their dysuria. Dr. Zimmerman, in his discussion, has explained the matter as well as it can be explained.

SOCIOECONOMIC ASPECTS OF DENTAL CARIES*

A Community and Individual Study of Dental Caries in Selectees

MAJOR ROBERT W. HYDE, M.C., A.U.S.†

WITH THE ASSISTANCE OF CORPORAL DANIEL J. O'CONNELL, A.U.S., AND CORPORAL GEORGE A. LENZI, A.U.S.,

BOSTON

IN SPITE of the fact that the study of dental caries lends itself with ease to a broad social approach, comparatively little work has been done with this form of investigation. The examination of selectees for induction into the armed forces includes a dental examination and thus furnishes for study an excellent cross section of the nation's male population of military age. During the first year of induction, dental rejections were reported as the highest single cause of disqualification for military service, with approximately 9.4 per cent of those examined found to possess insufficient teeth to meet the minimum standards.[1] An almost identical high rate of dental disqualifications (9.3 per cent) was found at the Boston Induction Station during the only comparable period. Studies were instituted at this station to determine what community socioeconomic factors were influential in this situation, and it is the purpose of this paper to set forth the results of these studies.

Klein and Palmer[2] have presented an excellent study of the influence of community socioeconomic conditions on the incidence of dental caries in urban children six to fourteen years of age in New Jersey. The present study concerns a very different group. It appears that the differences in methods and material between the two studies are so wide that if significantly similar results were obtained, it would serve to validate the conclusions of Klein and Palmer that the intrinsic tendency of children to develop dental caries does not depend on the socioeconomic status of the community in which they live, and that the volume of dental care in the form of filling of permanent teeth increases markedly with a rise in community socioeconomic status.

Studies by Britten[3] and Collins[4] showed that frequency of dental service varies greatly with socioeconomic status. Such studies are important only when considered with others showing the variation in dental defects that require dental care, for certain groups with low economic status may not be seeking dental care for the reason that they do not need it.

In none of these studies has any correlation been made between the rate of dental caries and that of dental deficiency of such degree that the subject is unable to subsist on the Army ration. A consideration of the incidence of caries may be far different from that of dental deficiency of such gross degree, wherein lack of reparative treatment rather than ability to resist caries may be the prime factor.

Classic studies made by Price[5] and Pickerill[6] have demonstrated the association of dental caries with the modern diet of civilized man and the almost complete absence of dental caries in all aborigines subsisting on native diets. Little has been shown, however, regarding the application of these studies to the variation in dental caries in the different races and nationalities now living in the United States.

It is not the purpose of this study to delve into the etiology of dental caries, but rather to present certain basic data necessary for the evaluation of preventive methods. Without knowledge of the relation of dental caries to community socioeconomic status and to nationality it is impossible to interpret findings on rates of dental caries.

SCOPE AND METHOD OF STUDY

The present study included the following factors: dental rejections in the examination of 60,000 consecutive selectees from twenty-one to thirty-eight years of age during the winter, spring and summer months of 1942; the decayed, missing and filled teeth in 3899 consecutive selectees from eighteen to thirty-eight years of age examined during a period of 1943; and the dental defects in foreign-born and first-generation Americans of the principal nationalities appearing in the examination of 2400 white and 1212 Negro selectees in a period of 1943.

The selectees were for the most part from urban backgrounds, since they came from the eastern segment of Massachusetts within about thirty miles of the seacoast. On the other hand, there were large enough areas beyond the large cities to make significant the number living in rural and semirural areas, such as would be found on Cape Cod.

The source of the selectees and the socioeconomic classification of the community from which they came were the same as those used in previous studies at this station of allergic states,[7] tuberculosis[8] and diabetes.[9] Hence, the rejection rates of these medical conditions furnish controls for comparison with dental rejections.

The social study was made of each community (local board) from which selectees came, and those factors were evaluated that were considered to be indicative of socioeconomic level. These factors were medical care, educational facilities, social class,

*From the Boston Armed Forces Induction Station.

†Medical director, Medical Section, Headquarters Boston Armed Forces Induction Station.

recreational facilities, public works, undesirably crowded housing and the welfare rate per capita. Each community was given a score on the basis of each of these factors, and the total score was called its "desirability rating." Communities of similar desirability ratings were grouped, so that all the communities fell into a six-category scale of desirability from A in the finest communities to F in the slum areas. For a more complete description of this method of social analysis, the reader may refer to one of our previous studies.[8]

Relation of Dental Rejections from Military Service to Community Desirability

The dental criteria for acceptance were relatively stable during the period in 1942 wherein 60,000 selectees were examined. For the greater part of the period the minimum requirement was an edentulous upper jaw and sufficient natural teeth in the lower jaw to support a partial denture.

The relation of the percentage of men rejected for military service to the desirability rating of the community from which they came is shown in Table 1. Although this relation is not entirely constant throughout the range, the percentage of disqualified persons ascends from 3.8 per cent in the best communities to 5.2 per cent in the poorest.

Table 1. *Relation of Percentage of Those Disqualified for Dental Defects to Community Desirabilty Rating.*

Community Desirability Rating	No. Examined	Percentage Disqualified for Dental Defects
A	6,300	3.8
B	6,100	2.8
C	16,800	4.7
D	15,200	4.6
E	9,400	4.6
F	6,200	5.2

The factors that possibly explain the greater rejection rate in the communities of low socioeconomic standing are less reparative dental care, poorer personal dental hygiene and poorer nutrition. If, however, Klein and Palmer are correct in stating that the incidence of caries is the same at all socioeconomic levels, the increased rejection rate is due to lack of reparative dental care at the lower socioeconomic levels. Hence, it is necessary to know whether dental disqualification from military service is an index of the amount of dental caries or of lack of reparative dental treatment.

Relation of Total Incidence of Caries Per Person to Community Socioeconomic Status

To ascertain the relation of total amount of dental caries to socioeconomic community status and thereby explain the true significance of dental disqualifications, a further study was undertaken wherein the number of decayed, missing and filled teeth per person was counted in selectees in each socioeconomic level. This group, consisting of 3899 men, differed from the previous group of 60,000 in that a greater proportion of men were eighteen to twenty years of age.

Figure 1 shows the average number of decayed (D), filled (F) and missing (M) teeth per person coming from communities of each desirability level, from the best to the poorest communities. The black

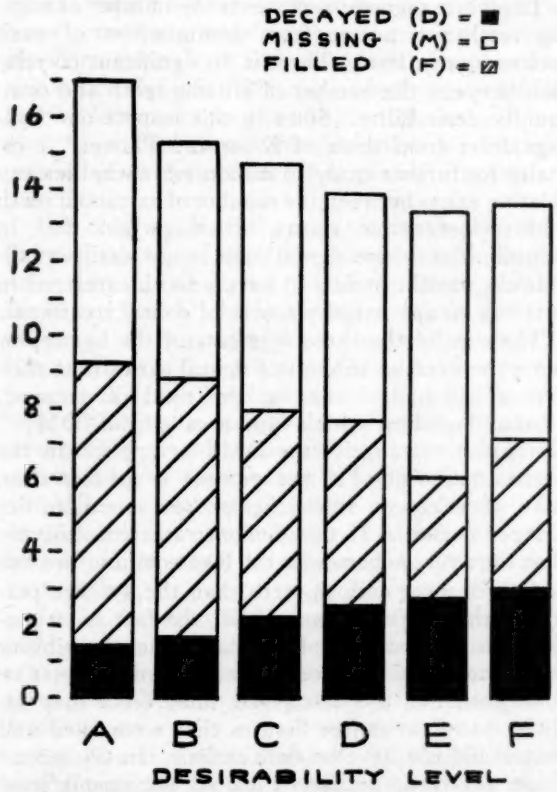

Figure 1. *The Relation of the Incidence of Dental Caries to the Level of Community Desirability.*

bars represent the number of decayed teeth per person found at the time of examination. There is an increase in decayed teeth from 1.5 per person in the best communities to over 3.0 in the poorest communities. Since it is obvious that a decayed tooth is evidence of lack of dental reparative care, it is clear that the need for dental care is present in all communities, but that in the poorer communities the need is twice as great as in the best ones.

The hatched segments indicate the number of filled teeth per person in each socioeconomic level. Here a striking contrast is shown, with about 8 filled teeth per person in the best communities decreasing to about 4 filled teeth per person in the poorest communities. Here can be seen the abundance of dental fillings in persons of every socioeconomic level and their increase with improvement of this level. The number of filled teeth per person appears to be a true representation of the variation in amount of

reparative dental care at different socioeconomic levels, so that it can be considered that dental care is twice as extensive in the best as in the poorest communities. This is in general agreement with the findings of Collins[4] and of Britten,[3] although they approached the problem from the angle of investigating the amount of care received. Our study, however, has the advantage of associating care received with the need for care.

The white segment represents the number of missing teeth per person from communities of each socioeconomic level. There is no significant correlation between the number of missing teeth and community desirability. Since in this respect our findings differ from those of Klein and Palmer,[2] it remains for further study to demonstrate whether any relation exists between the number of extracted teeth and socioeconomic status. It is certain that in communities where dental care is not easily available the patient prefers to have a tooth extracted to entering on any lengthy course of dental treatment.

The sum of the three segments of the bar represents the average amount of dental caries that each person has had, — that is, the total of decayed, filled and missing teeth,— and is called the "DMF." Here, quite strangely, the DMF per person in the best communities (17 per person) is greater than that of selectees from the poorest communities (14 per person). If this demonstrates conclusively that the average person in the best communities has had three more carious teeth than the average person in the poorest communities, the fact is of considerable importance. Before any such possibility can be accepted, however, two alternatives must be considered. In the first place, filled teeth may include many caries-free fissures that were filled and that would not have become carious.[7] In the second place, the communities of low socioeconomic level contain a somewhat larger percentage of foreign-born and of races with better teeth than the American average.

If neither of these suggestions proves adequate to explain the increased incidence of dental caries in the better classes, it follows that: the supposedly superior nutrition of the better socioeconomic levels may be poorer nutrition from the dental point of view; that the more extensive personal dental hygiene practiced in the better communities may be injurious; and that the work of dentists may even be responsible for the increased DMF. Perhaps if the findings of Price[5] and Pickerill[6] that dental caries is experienced by civilized man on modern dietaries are considered, it can be assumed that the rating of socioeconomic level in this study conforms in some degree to civilization and that the best communities contain persons with more civilized modern dietary habits than those in Group F and hence with worse teeth.

It can at least be said that the people from poor communities have had no more dental caries than do those from well-to-do communities. This conclusion and our findings on the relation of carious teeth and filled teeth to community socioeconomic level are in accord with the findings of Klein and Palmer.[2]

This study of the relation of DMF to socioeconomic level shows that dental requirements are so low that the rejections because of dental defects are more indicative of gross lack of reparative dental care than of the amount of dental decay. This shows that dental care is fulfilling a worthy role, but that the role is the repair of teeth, not the prevention of caries.

Relation of Dental Caries to Nationality and Race

A study was made of the composition of each community (local board) by nationality. Only those communities were considered in this study wherein there was a predominant nationality. Although a community study of nationality has the intrinsic fault of including a minority of persons of other nationalities, it has the advantage of considering those of the same nationality who have grouped themselves and thus have preserved more of their original culture and habits, including dietary habits, than they would otherwise have done.

Table 2 represents the number of men disqualified for military service because of dental deficiency who resided in communities with a predominant nationality in the first (1942) study of 60,000 examined selectees. In the Irish communities three times as many persons (6.8 per cent) were disqualified for military service because of dental defects as in the Portuguese (2.0 per cent) and Russian-Jewish communities (1.9 per cent). Since this is a far wider variation in dental rejections than that considered in Table 1, wherein the relation to socioeconomic status is considered, it becomes important to study dental caries in its relation to nationality. As has already been shown in the consideration of DMF and socioeconomic status, the variations in dental disqualifications according to nationality cannot be considered as primarily indicative of caries but rather as showing the proportion of persons with gross dental defects who have not had reparative dental care. With three times as many persons in certain communities as in others having dental deficiency of such a gross degree that it is disqualifying for military service, the need for community planning of dental care is suggested.

Table 2. *Percentage of Persons Disqualified for Dental Defects from Communities with a Predominant Nationality.*

Predominant Community Nationality	No. Examined	Percentage Disqualified
Irish	2440	6.8
English-speaking foreign and old American	1640	4.4
Italian	3472	4.1
Portuguese	2406	2.0
Jewish (Russian)	1869	1.9

The study of the relation of the rate of dental caries to nationality differs from this community study of relation of dental rejections to dominant community nationality in that each person is of the nationality specified, so that there are included persons living in Americanized communities who have lost some of their national dietary habits.

Figure 2 shows the relation of decayed, filled and missing teeth and to nationality by parents' birthplace. A wide variation is seen in all factors. The

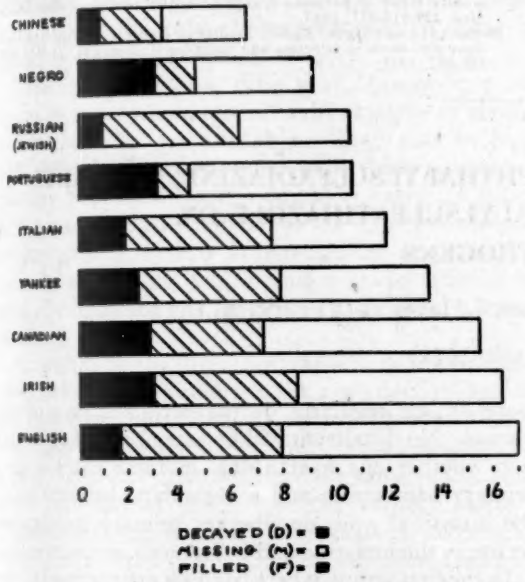

FIGURE 2. *The Relation of the Incidence of Dental Caries to Nationality.*

number of decayed teeth found at the time of examination ranged from an average of less than 1 per person in the Chinese and Russian (Jewish) groups to over 3 per person in the Irish and Portuguese groups. Here, the lack of relation of the number of decayed teeth found at time of examination (D) to the total number that had been decayed at some time (DMF) is especially noteworthy, with the Portuguese and Irish having had very different amounts of decay but nearly the same total number of decayed teeth (DMF).

The number of filled teeth per person also varied greatly with nationality. The Portuguese had the lowest number, 1 filled tooth per person; and the Negroes came next with less than 2 filled teeth per person. Both Negroes and Portuguese also had a comparatively high number of decayed teeth but a low number of teeth that had been attacked at some time by decay. Thus, two peoples with extremely inadequate dental care, as shown by such a high rate of decayed teeth and low rate of filled teeth, had far less dental decay than the average. This again shows that the nationalities having the least dental care may have the least dental caries. Most of the other groups had high numbers of filled teeth: Russian (Jewish), Italian, old American, Canadian, Irish and English all having on the average more than 4 filled teeth per person.

The number of missing teeth per person appears to bear a rough relation to the number of teeth that have at some time decayed (DMF). It decreases from a high rate of 8.5 missing teeth per person in the English, with a DMF of 17.0 to 3 per person in the Chinese, with a DMF of 6.5. No relation can be seen between missing teeth and either decayed or filled teeth. The only nationality wherein there was a comparatively large number of missing teeth was the Portuguese, with 5.8 missing teeth per person and a low DMF (10.5). This may possibly be explained by the fact that many of the Portuguese come from rural Cape Cod areas, where dental care may be less accessible or the cultural background may be comparatively low.

The total amount of caries that each person had ranged from over 15.5 per person in the English, Irish and Canadians to 10.5 in the Portuguese and Russian (Jewish), 9.5 in the Negroes and 6.8 in the Chinese. As has already been shown in comparing the numbers of decayed and of filled teeth, the total amount of caries is independent of dental care. This wide difference in dental decay in different nationalities is important because it shows the insignificant place of dental care in dental decay and presents a valuable angle of attack on the problem of etiology of dental caries. Furthermore, it shows that prevalence figures must be corrected on the basis of nationality.

For explanation the factors of both heredity and culture require consideration. Either there is an inherent difference in racial susceptibility to caries or there is a difference in the dietary habits of the different races.

Price[5] and Pickerill[6] have established beyond doubt that the teeth of aborigines, almost perfect while on their native dietary, become carious when they change to the modern civilized dietary. This suggests that the element of racial susceptibility is entirely secondary to dietary habits, although further study may be required to demonstrate this conclusively.

SUMMARY

Studies were made of dental defects found in the examination of selectees at Boston Armed Forces Induction District and the relation of dental defects to nationality and the socioeconomic background of the communities from which these selectees came.

The incidence of total caries (decayed, missing and filled teeth) per person was found to be highest in the best communities and lowest in the poorest, whereas the number of filled teeth decreased consistently from the best to the poorest communities, reflecting the consistent effect of socioeconomic status on reparative dental care.

The fact that more men from the poorer communities than from the best ones were rejected for

insufficient teeth is more indicative of lack of reparative care than of the amount of dental decay that they had had.

The English and Irish had had the greatest amount of dental decay, whereas the Negroes and Chinese had the least. This fact was not dependent on dental care, since the English had a great number of filled teeth and a small number of decayed teeth, whereas the Negroes had a large number of decayed teeth and few filled teeth. Three times as many selectees from Irish communities were rejected because of dental defectiveness as from Portuguese or Russian (Jewish) communities.

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IN VITRO ACTION OF SULFAMERAZINE, PHTHALYLSULFADIAZINE, PHTHALYLSULFAMERAZINE AND PHTHALYLSULFATHIAZOLE ON ENTERIC PATHOGENS

Fritz B. Schweinburg, M.D.,* and I. Jacques Yetwin, M.D.†

Waltham, Massachusetts

THE sulfonamides have produced clinical results beyond expectation. These drugs were first directed against the septicemias, especially streptococcal and pneumococcal infections. The attention of investigators later centered on infections due to other bacteria, notably those of the pathogenic intestinal group. Relatively little work has been done on the direct effects of the sulfonamide drugs on intestinal bacteria and most of the available literature deals with their clinical effects. The preponderance of clinical studies is justified and is the most important consideration for both patient and practitioner.

In most conditions where the sulfonamides are employed, the blood level of the drug — usually administered by mouth — if kept at a satisfactory concentration for the desired time seems to be responsible for the beneficial effects. The ability of a drug to be absorbed from the intestine in an amount sufficiently high to maintain a proper blood level is especially noted in diseases where a septicemia or bacteremia is manifested. This is particularly true in infections with streptococci, pneumococci, meningococci and the like.

The situation is different when one considers the possible effects of these drugs in infections where the gastrointestinal tract is the main site of the disease or pathologic changes. In such cases one may differentiate two large groups of intestinal diseases: those in which bacteria responsible for the disease are restricted to the intestinal wall, no bacteremia occurring at any time and those in which, in addition to the local intestinal changes, a bacteremia occurs more or less regularly during certain stages of the disease. No discussion will be attempted of the question whether one has to deal in these cases with a primary bacteremia and a secondary localization in the intestinal wall, or whether primary localization occurs in the intestine and is followed by bacteremia.

In the first group, where bacteria are confined to the intestinal wall, the resultant diseases are caused by the different Shigellas or by *Vibrio comma*. In the group where bacteremia occurs regularly, they are produced by members of the typhoid-paratyphoid group, *Eberthella typhosa* and the Salmonellas. The infrequent intestinal infections with *Bacillus anthracis*, with the Brucellas, with *Pasteurella tularensis* and with *P. pestis* should theoretically be included in the latter group.

It is apparent that the effects of the drugs on these dissimilar groups of enteric infections must depend on entirely different qualities inherent in them. If the bacteria are restricted to the intestinal tract, it is more appropriate to choose drugs that have a slow rate of absorption and remain in the intestine in effective concentration. In the second group, drugs must overwhelm the bacteria in the intestine as well as in the general circulation. Here, a drug with good but not too rapid absorption should be chosen, or even a combination of two different drugs may be administered. One of these should be easily absorbed, thus combating the bacteria in the circulation, whereas the other should be poorly absorbed, thus acting on bacteria in the intestinal lumen and wall.

Aside from the problem mentioned in the preceding paragraphs, the action of the various sulfonamides on the separate pathogenic bacteria should be known in detail. Owing to mutual chemical affinities, even

*Professor of bacteriology, Middlesex University School of Medicine, Waltham, Massachusetts.

†Associate professor of parasitology, Middlesex University School of Medicine.

slight changes in the composition of a given drug may alter its effects on various bacteria; it may become more useful in the destruction of one bacterium and less useful in that of another. It is fully realized that any conclusions drawn from the following experiments can cover only one — and perhaps not the most important — part of the story. Investigations made in vitro enable one to determine the immediate effect of a given drug on a given bacterium, but do not decide which drug is most useful clinically in a given disease. The questions of rapid or slow absorption, of producing and maintaining an appropriate blood level and of the rate of drug excretion cannot be solved by test-tube studies.

Experiments of this type may, however, prove useful in cases where several sulfonamides of similar absorption rates are available. They may be especially useful when performed with those pathogenic bacteria that exert their principal or exclusive action on the intestinal tract. So far as the intestinal diseases are concerned, there is apparently no unanimity of opinion concerning which sulfonamides should be used in combating the particular pathogenic bacteria involved.

According to the literature, there is no doubt whatsoever that some sulfonamides are effective against the dysenteric infections. It seems, however, that in infections with bacteria of the typhoid-paratyphoid group the effects of such drugs are not proved, since some difference of opinion on the subject exists.[1–6] These doubts, together with other reasons, account for the preparation of numerous new sulfonamides in the hope of finding a new compound that will prove effective in cases in which the older drugs have failed. This is laudable work, and any opportunity to evaluate a new drug and to determine its worth against certain bacteria is most welcome. We are therefore indebted to Dr. E. L. Burbidge of Sharp and Dohme, Incorporated, Philadelphia, for supplying us with four new sulfonamides.

So far as we know, only one of these drugs, sulfamerazine, is under clinical investigation; a few reports of its use have already appeared.[7–15] A similar sulfonamide with two methyl groups, sulfamethazine, has been tested clinically by three groups of investigators, with results comparable to those obtained with sulfamerazine.[16–18] Nothing has as yet been published on the other three drugs. These preparations were obtained during studies on several older well-known compounds for their effects on various enteric organisms. References in this paper are restricted to in vitro studies made against the intestinal organisms.[19–28]

The opportunity has thus been given to compare the effects of the new drugs on certain bacteria with the effects of the older drugs from which they are derived. At the present time all that will be done is to state briefly what the in vitro effects of the new drugs are on representative species of intestinal bacteria. Perhaps this will serve to expedite clinical applications that may follow.

Materials and Technic

The chemical structures of the drugs at our disposal were as follows:

Sulfamerazine is sulfa-methyl-pyrimidine or 2-sulfanilamido-4-methylpyrimidine. It is monomethylated sulfadiazine, but has some characteristics peculiar to the specific compound. Tests show that it is more readily soluble, more quickly and more fully absorbed and less rapidly excreted than is sulfadiazine.[8]

Phthalylsulfamerazine is sulfamerazine to which a phthalyl radical has been added.

Phthalylsulfadiazine is sulfadiazine to which a phthalyl radical has been added.

Phthalylsulfathiazole is sulfathiazole to which a phthalyl radical has been added.

These drugs are crystalline white powders, sparingly soluble in water. Solutions were prepared in sterile nutrient broth. In no case was it possible to obtain clear solutions above a concentration of two per cent. Even at this concentration sulfamerazine and phthalylsulfathiazole did not dissolve readily unless the container was gently heated. In a few cases it was found necessary to heat the stock solution just before use because of a slight amount of sedimentation. It occurred to us that heating might increase the concentration of the drug to a slight extent, but we believed the increase to be negligible. We attempted to minimize this effect by preparing only small amounts of the drugs at a given time.

Since it is known that the solubility of sulfonamides in water — and consequently in nutrient broth — increases with a rising pH, working with strong basic solutions would have been advantageous. But the alkalinity of the solutions was limited by the fact that the medium had to be favorable for bacterial growth. It was decided to maintain a pH of 7.6 in all dilutions throughout the course of the experimentation, using a few drops of 10 per cent sodium hydroxide to aid solution of the drug and to obtain the proper reaction. Lower concentrations were prepared by diluting the 2 per cent solution with necessary amounts of nutrient broth at pH 7.6. Routine solutions were concentrations of 2.0, 1.5, 1.0, 0.50, 0.25, 0.10, 0.05, 0.025 and 0.010 per cent.

The following bacteria were tested in these series: *Escherichia coli*, *Eberthella typhosa*, *Salmonella paratyphi*, *S. schottmülleri*, *S. enteritidis*, *S. suipestifer*, *Shigella dysenteriae* (Shiga), *Shig. paradysenteriae* var. *Flexner*, *Shig. paradysenteriae* var. *Hiss* and *Shig. sonnei*. A standard loop of each bacterium was taken from a twenty-four-hour slant on agar, transferred into 5 cc. of nutrient broth (pH 7.6) and incubated for twenty-four hours. The degree of cloudiness after this period of time varied with each organism.

In order to have approximately the same number of bacteria in all tubes, the twenty-four-hour cultures were standardized with a nephelometer. The neph-

elometer tubes were originally standardized against a twenty-four-hour growth of *E. typhosa*. By plating out and counting the ten different strains, it was determined that the nephelometer reading for *E. typhosa* could be used as well for the standardization of the other nine organisms, the percentage of error being practically zero. Consequently, all twenty-four-hour broth cultures were standardized against a tube of the nephelometer corresponding to a count of 16,000,000 bacteria per cubic centimeter. Some slight errors are possible in this method of standardization, but it was thought certain that a few thousand bacteria more or less would in no way alter the results of the experiments. The findings obtained in the series later proved this assumption to be correct.

TABLE 1. *Sample Protocol.*

Organism: *E. typhosa* Protocol: 36
Drug: Phthalylsulfathiazole
Tubes inoculated: 2-2-43 Plates made: 2-3-43

Concentration of Drug	Cloudiness of Tubes	Dilution used	Endo Plates count plate 1	Endo Plates count plate 2
%				
2.0	Clear	Whole	0	0
1.5	Clear	Whole	0	0
1.0	Trace (?)	Whole	60	0
0.50	Trace	1:1000	225	0
0.25	Moderate	1:2000	575	90
0.10	Moderate	1:2000	810	200
0.05	Heavy	1:4000	Innumerable	1220
0.025	Heavy	1:4000	Innumerable	1270
0.010	Heavy	1:4000	Innumerable	1230
None (control)	Heavy	1:4000	Innumerable	1250

A 1:100 dilution of each standardized suspension was made in physiologic saline solution just prior to use. One tenth of a cubic centimeter of this dilution was added to 0.9 cc. of the respective drug dilution, so that each tube always contained the same number of bacteria (16,000 per cubic centimeter). All tubes were incubated for twenty-four hours and read for degree of cloudiness. Following this, appropriate dilutions of the growth were plated out on Endo's agar. After a few preliminary trials it was learned which dilutions were satisfactory in order to obtain a countable number of colonies on the plates. One tenth of one cubic centimeter of the respective dilution was always plated out, two plates being streaked with the same glass rod. In this manner there was regularly obtained a countable number of colonies on at least one of the plates after incubating them for twenty-four hours. As a control, a similar amount of bacteria was inoculated into 0.9 cc. of broth and twenty-four hours later plated out in the manner described above. It was thus possible to discover by comparison any slight bacteriostatic effect of the drug concerned. A sample protocol is shown in Table I.

Experimental Results

The experimental findings are listed in Table 2. The percentage noted in each column reveals the lowest concentration of the respective drug that produced the indicated effect. Each figure represents the average of ten complete trials. Any differences that were found among the separate trials never exceeded one tube higher or lower in concentration and were exceedingly rare.

Discussion

Several results are apparent from Table 2.

Sulfamerazine is effective against *Esch. coli* in vitro in a concentration of 2 per cent; the other three drugs are bactericidal only at concentrations above 2 per cent. The same drug is bacteriostatic for this organism at a concentration of 0.1 per cent, whereas the others fall between 1 and 2 per cent.

Phthalylsulfathiazole is the best bactericide against *E. typhosa*, being effective at 1.5 per cent, and it is bacteriostatic at 0.5 per cent. The other drugs range in bactericidal power from 2.0 to over 2.0 per cent, and in bacteriostatic effect from 1 to over 2 per cent. The superiority of phthalylsulfathiazole over the other three drugs is fully evident.

Against *S. paratyphi* phthalylsulfathiazole is bactericidal at 2 per cent, with the other drugs going above that concentration. For bacteriostatic action, both sulfamerazine and phthalylsulfadiazine are effective at 1 per cent, whereas the others are effective above 1.5 per cent.

Sulfamerazine is the most effective bactericide against *S. schottmülleri*, killing at 2.0 per cent, and together with phthalylsulfathiazole is effective as a bacteriostatic agent at 1 per cent.

Sulfamerazine and phthalylsulfadiazine are equally effective as bactericides against *S. enteritidis* at 1.5 per cent. Together with phthalylsulfathiazole, all three are bacteriostatic at 0.1 per cent.

Against *S. suipestifer* the best bactericide is phthalylsulfathiazole (1.5 per cent). The best bacteriostatic agents are sulfamerazine and phthalylsulfadiazine (0.5 per cent).

TABLE 2. *Bactericidal and Bacteriostatic Action of the Sulfonamides on Various Intestinal Bacteria.*

Organism	Action	Sulfamerazine	Phthalylsulfadiazine	Phthalylsulfamerazine	Phthalylsulfathiazole
		%	%	%	%
Esch. coli	A	2.0	2.0+	2.0+	2.0+
	B	0.1	1.5	2.0	1.0
E. typhosa	A	2.0	2.0+	2.0+	1.5
	B	1.0	2.0	2.0+	0.5
S. paratyphi	A	2.0+	2.0+	2.0+	2.0
	B	1.0	1.0	2.0+	1.5
S. schottmülleri	A	2.0	2.0+	2.0+	2.0+
	B	1.0	2.0	2.0+	1.0
S. enteritidis	A	1.5	1.5	2.0+	2.0
	B	0.1	0.1	0.5	0.1
S. suipestifer	A	2.0+	2.0	2.0+	1.5
	B	0.5	0.5	2.0	1.0
Shig. dysenteriae	A	0.1	0.5	1.0	0.5
	B	0.05	0.1	0.1	0.1
Shig. paradysenteriae var. *Flexner*	A	1.5	1.0	2.0	0.5
	B	0.05	0.1	0.1	0.05
Shig. paradysenteriae var. *Hiss*	A	2.0	1.0	2.0+	2.0+
	B	1.0	1.0	2.0	1.0
Shig. sonnei	A	1.5	1.0	2.0	1.5
	B	0.5	0.5	1.5	0.5

A = bactericidal concentration (complete destruction of bacteria).
B = bacteriostatic concentration (partial inhibition of growth as compared with control tube).

Each of the various strains of Shigella differs with respect to the bactericidal and bacteriostatic actions of the four drugs studied. The Shiga strain is destroyed by sulfamerazine at 0.1 per cent, the same drug being effective as a bacteriostatic agent at 0.05 per cent. The Flexner strain is killed by phthalylsulfathiazole at 0.5 per cent; the same drug, and also sulfamerazine, are bacteriostatic as low as 0.05 per cent.

A concentration of 1 per cent phthalylsulfadiazine proved to be bactericidal for the Hiss and Sonne strains, but the highest bacteriostatic effects are equally divided among sulfamerazine, phthalylsulfadiazine and phthalylsulfathiazole. These three drugs are bacteriostatic for the Hiss strain at 1 per cent and for the Sonne strain at 0.5 per cent.

From the results obtained on four hundred experiments with these four drugs and by comparison with the eight hundred protocols already obtained on the older sulfonamides, the following conclusions may be readily drawn:

Sulfamerazine is better than sulfadiazine when used in vitro against *S. enteritidis*, *S. suipestifer* and the Shiga and Sonne strains of Shigella. Sulfadiazine is a better bactericidal and bacteriostatic agent than is sulfamerazine when used against *E. typhosa*, *S. paratyphi*, *S. schottmülleri* and *Esch. coli*. Both drugs have similar bactericidal and bacteriostatic effects on the Hiss and Flexner strains of Shigella. The addition of the methyl group to sulfadiazine therefore makes it more effective chiefly against the dysentery organisms, but weakens its actions against some of the others in vitro.

Phthalylsulfadiazine is better than sulfadiazine when used against *S. enteritidis* and the Hiss, Flexner and Sonne strains of Shigella, but the reverse is true when these drugs are used against *E. typhosa*, *S. paratyphi*, *S. schottmülleri*, *S. suipestifer* and *Esch. coli*. Both drugs are equally effective against the Shiga strain. The addition of the phthalyl radical to sulfadiazine makes it more effective for most of the dysentery organisms and for *S. enteritidis* in vitro.

Sulfamerazine is decidedly better as a bactericide and bacteriostatic agent than is phthalylsulfamerazine against *all* the organisms studied. The addition of a phthalyl group to this particular drug diminishes the effective action of the sulfamerazine in vitro.

Phthalylsulfathiazole has a better bactericidal action than has sulfathiazole when used against *E. typhosa* and the Flexner strain of Shigella; it is also a better bacteriostatic agent against *S. enteritidis*. As bactericides both are equally effective against *S. enteritidis*, *S. suipestifer* and *Shig. sonnei*. Against *Esch. coli*, both paratyphoid species and the Hiss and Shiga strains of Shigella, phthalylsulfathiazole is much weaker, both as a bactericide and a bacteriostatic agent, than sulfathiazole.

The tabulation indicates that the best bactericidal and the best bacteriostatic effects on each organism examined are not always produced by the same drug. It is also apparent that, at least in vitro, the addition of the phthalyl group serves some limited advantage with sulfadiazine and sulfathiazole against certain bacteria. It actually diminishes the effective power of sulfamerazine for all bacteria studied. This observation, of course, does not necessarily mean that the actions in vivo are also lessened by the addition of the phthalyl radical. Since the attached radical is easily split from various compounds,[29] it is most likely set free in vivo, so that the end effects may be identical with those produced by the simpler sulfonamides. This question can be answered only by animal experimentation.

The results were obtained by testing one strain only of each of the organisms, otherwise the technical work would have extended beyond the facilities at our disposal. Helmholz[30] has shown for *Esch. coli* that different strains of this organism exhibit different resistances against concentrations of the same drug in urine. Possibly by testing more strains of a single type of organism the results would have been slightly altered. Since some of the differences demonstrated were so striking and so constant, however, we believe that the results may be considered valid.

Summary

Four new sulfonamide drugs — sulfamerazine, phthalylsulfadiazine, phthalylsulfamerazine and phthalylsulfathiazole — were tested for their in vitro action on certain enteric pathogens.

From the results obtained, it is apparent that, as with the older sulfonamide compounds, the Shigellas are more susceptible to bactericidal and bacteriostatic action in vitro than are strains representative of other genera.

In certain instances, the new compounds were found to be more effective in vitro than the older compounds, whereas in others, the reverse was found to be true.

We are indebted to Miss Marian Land for technical assistance furnished during these studies.

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MEDICAL PROGRESS

HEMATOLOGY

WILLIAM DAMESHEK, M.D.*

BOSTON

DURING war, research in subjects not directly connected with military medicine must naturally become greatly restricted. Because of this, publications in the field of hematology have been fewer in number, but many of these are of immediate practical value. In line with these new conditions, this year's review will be limited to a discussion of three subjects: blood transfusions and blood substitutes, hemorrhagic diseases and hemolytic processes.

BLOOD TRANSFUSIONS AND BLOOD SUBSTITUTES

The Russian Contribution

Bagdasarov[1] reviews the development of the Russian system of blood storage and distribution, in many respects the forerunner of the blood and plasma banks of today. Perhaps realizing the imminence of a new world conflict, the Russians in 1927 set up the Central Institute for Blood Transfusion in Moscow, with separate decentralized institutes in various cities. By 1932, eighty of these institutes were in active operation for the distribution of blood to the surrounding communities and for active research in methods for the preservation, administration and storage of fresh and cadaver blood. The Spanish Civil War served as a perfect setup for the clinical application of these studies. It was found that a mixture of citrate and glucose was a better preservative than citrate alone, that the universal donor could be used on a large scale in the front lines without further typing or cross matching, and that undue hemolysis in transportation could be prevented by the use of isothermic containers, which were best transported by the airplane rather than by truck or train. The use of plasma in Russia has lagged behind that in this country and Britain, perhaps because every available soldier and noncombatant at or close to the fighting zone has served as a volunteer donor. The red-cell mass, a by-product of plasma preparation (see below), has been routinely used in cases of severe hemorrhage. A somewhat mysterious note in Bagdasarov's review is that regarding "physiological balanced solutions," which contain a certain amount of plasma in an alcohol-and-glucose-solution base. This cocktail-like infusion is said to reinforce the vital processes, especially when the wounded patient suffers from disturbed hemodynamics not associated with severe blood loss and in septic cases. Although not strictly apropos, mention may here be made of the development by Bogomolets[2] of A. C. S. (anti-reticular cytotoxic serum), with spleen and bone marrow used as antigenic substances. The resulting serum injected in small doses is said to enhance greatly the immune activities of the reticuloendothelial cells and thus help such diverse conditions as frostbite, slowly

*Professor of clinical medicine, Tufts College Medical School; visiting physician and consulting hematologist, Joseph H. Pratt Diagnostic Hospital.

healing infections, typhus fever and many others. Bogomolets also believes that it may reduce the normal aging process.

Blood Groups, Agglutinins and So Forth

Methods. The use of high titer serum, which is now readily obtainable, should be routine. Serum concentrates,[3] powdered serum* and serum and plasma fractions[4] are all being developed and have their specialized indications. Powders keep well in a wide temperature range and give an extremely quick reaction that can be readily seen on the slide with the naked eye. Since the globulin fraction of serum or plasma contains all the enzymatic factors and antibodies, including agglutinins, methods for its separation from the albumin fraction have been developed. Thus, Pillemer[4] precipitates the albumin with methyl alcohol and concentrates the globulin fraction; the agglutinin content of this material is extremely high. This work has been continued in the laboratory of Dr. E. J. Cohn at the Harvard Medical School under contract with the Committee on Medical Research of the Office of Scientific Research and Development and in collaboration with the Division of Blood Research, Army Medical School.[5]

The slide test is adequate for ordinary typing, but it should not be relied on for cross-matching purposes, since it is relatively insensitive, particularly for weakly reacting and "warm" agglutinins, including the anti-Rh agglutinin. As emphasized in previous reviews, the Landsteiner–Levine test-tube technic is far more accurate and should become a routine procedure.

Under this method, small test tubes (7 by 75 to 100 mm. — that is, Hinton or Kahn tubes) are used. One drop of the serum to be tested, 2 drops of a 2 per cent red-cell suspension and 1 drop of normal salt solution are placed in the tube, mixed and placed in the incubator remaining there for at least thirty minutes. The tube is removed and centrifuged at extremely slow speed for one minute. The "button" may be examined with a hand lens for the presence or absence of agglutination. The tube is then shaken and examined for macroscopic agglutination. Confirmation of the presence or absence of agglutination is obtained by examination of some of the tube's contents on a slide with the low power of the microscope. This method, although seemingly complicated in its description, is readily performed in simple laboratory setups and is sufficiently sensitive for the detection of the great majority of normal and abnormal agglutinins of low titer, including the anti-Rh agglutinin.

The one possible disadvantage of the routine use of the above technic is that it fails to detect cold agglutinins, which have recently assumed some diagnostic importance. This disadvantage may be obviated by performing simultaneous compatibility tests at either room or, preferably, icebox temperature. For routine transfusions, it matters little whether the recipient's blood contains a cold agglutinin, provided that relatively warm blood is used; however, the finding of incompatibility owing to the appearance of agglutination in the slide-cross-matching technic at *room* temperature has often held up the use of transfusion in patients desperately ill with acute hemolytic anemia.

Rh agglutinogen and anti-Rh agglutinin. The development of knowledge regarding the Rh factor (agglutinogen) and its relation to transfusion reactions and to acute hemolytic anemia of the newborn (erythroblastosis fetalis) has made one of the most fascinating and important chapters in modern medicine. This has been duly recorded in previous reviews. The correctness of Levine's original assumption that erythroblastosis fetalis is due to the development by an Rh− mother of an anti-Rh agglutinin, with resultant effects on the fetus's Rh+ cells, has been borne out in at least 90 per cent of all cases. Other agglutinins, or even such physical factors as the condition of the placenta, may have some bearing in a few cases. The failure of some infants born of Rh−, Rh+ matings to develop acute hemolytic anemia may depend on the father's genotype: that is, an Rh+ phenotype is made up of either genotypes RhRh or Rhrh. From the latter genotype, the infant may inherit either dominant Rh or recessive rh. If the latter, the union of recessive gene rh with the mother's rh results in an Rh− infant's blood.[6]

The low incidence of erythroblastosis fetalis in Negroes and Chinese led Levine and Wong[7] to study the incidence of the Rh factor in these groups. Although 15 per cent of Whites are Rh−, only 5 to 8 per cent of the Negroes tested were Rh−, and only 1 of the 150 Chinese tested was Rh−. (It should be pointed out to those who pride themselves on the lack of the "monkey" factor in their red cells that its absence does not necessarily preclude the possibility of the presence of, say, a baboon or an orangutan factor. Studies of human blood for such factors have not yet been undertaken.)

Determination of the Rh factor is of importance in at least three conditions: in pregnancy and childbirth when a transfusion is contemplated for severe anemia or shock, in acute hemolytic anemia of the newborn and in repeated transfusions. In the last if the recipient is Rh−, repeated transfusions of blood, even of the same group, will almost certainly result in the development of an anti-Rh agglutinin; thus, after three to six or more transfusions, the next transfusion if consisting of Rh+ blood may result in a severe and perhaps fatal hemolytic reaction.[8]

For determination of the Rh factor, a potent anti-Rh serum must be available. As yet, such serums are difficult to obtain, because the regular production of potent anti-Rh agglutinin in animals has proved

*Prepared by Lederle Laboratories, Incorporated, Pearl River, New York.

extremely difficult and because high-titer anti-Rh serums are only occasionally found in the mothers of infants with erythroblastosis fetalis. It is advised that each mother of such an infant be routinely tested for anti-Rh agglutinin and that if this is present, even at low titer, she be bled 50 to 100 cc. Concentration of serum can later be performed. Methods for doing this are now in process of development.

The test for the Rh factor is performed by the Landsteiner–Levine technic at 37°C., as above described. It is important to use dilute — 1 to 2 per cent — red-cell suspensions. Levine[6] and his coworkers have found three types of anti-Rh serum, one agglutinating 87 per cent of the red cells of white persons (anti-Rh_1 and anti-Rh_2), another agglutinating 85 per cent (anti-Rh_1) and the third agglutinating 73 per cent (anti-Rh_2). Since the last serum gives 27 per cent negative reactions, the significance of an Rh− determination in a given case is open to doubt. Thus, unless a laboratory has a highly potent anti-Rh testing serum, it is important to perform a careful compatibility test of the recipient's serum with the prospective donor's red cells. To do this, the time of incubation should be prolonged to one hour. Boorman, Dodd and Mollison[9] suggest a modification of Levine's technic, which they state brings out more clearly the anti-Rh agglutinin. These workers allow the mixture of recipient's serum, donor's red cells and normal salt solution to remain in the incubator for two hours. The pattern of the sediment is then examined with a hand lens and a portion is pipetted off for microscopic examination. They state that the manipulation of the blood involved in centrifugation and shaking may abolish a weak reaction. If such tests are negative, the transfusion may be given with almost complete safety. The reservation must nevertheless be made that even with a completely negative in vitro test, there may be an in vivo hemolytic reaction. The only possible way to obviate this completely is to set up a list of well-established Rh− donors for use in the three conditions referred to above — that is, in women in childbirth, in cases of erythroblastosis fetalis and with repeated transfusions. It is almost essential to use nothing but Rh− blood in infants with acute hemolytic anemia, since transfusions are the only treatment, and the introduction of Rh+ cells may result in the combination with any still present anti-Rh agglutinin derived from the mother.

Cold hemagglutinins. The antigen-antibody reaction between human red cells and serum that is observed chiefly or solely at temperatures below 20°C. is called "cold hemagglutination." Cold agglutinins in low titer are commonly present. Thus, Kettel[10] found them in 95 per cent of normal subjects, and more recently Shooter[11] in examining 4710 serums observed that 32 per cent showed these antibodies at 5 to 7°C. Cold agglutinins sufficiently strong to be active at room temperature were found, however, in only 29 of 10,000 serums. Low temperatures at times activate or bring to light an otherwise weak agglutinin; this is reminiscent of the Donath-Landsteiner phenomenon — the activation by cold of the abnormal hemolysin of paroxysmal cold hemoglobinuria. The subject of cold hemagglutination is an old one, having been discussed by Landsteiner in 1903 and more fully by Landsteiner and Witt in 1926.* Although cold hemagglutinins have been observed in such diverse diseases as cirrhosis of the liver, hemolytic anemia of the acquired type and infections due to spirilla and trypanosomes, interest in this subject has been considerably enhanced in the past year by the finding of such agglutinins of high titer in primary atypical (virus ?) pneumonia.[13,14] The initial hope that this antibody would prove of diagnostic importance in the differentiation of atypical and other pneumonias has proved only partially correct, since a fairly high titer is present initially in only about 50 per cent of all cases. The titer of agglutinin frequently increases with progression of the disease and may not reach its peak for seven to twenty-one days.[15]

The cold hemagglutinin appears to be quite distinct from the normal blood agglutinins, since it agglutinates all human red cells, even those of Group O, and may agglutinate those of a number of animals — that is, "pan-agglutinin." Because it also has the property of agglutinating the red cells of its own blood,— at least in the test tube,— the term "autoagglutinin" has often been used. This, however, is only partly descriptive and it is probably best to use the more general term "cold hemagglutinin."

Aside from its purely diagnostic significance, the cold hemagglutinin has recently assumed considerable clinical importance. Thus, certain cases of acute hemolytic anemia occur at times in association with primary atypical pneumonia. Usually the sulfonamide drugs have been administered and it has been customary to ascribe the hemolytic reaction to the drug. Whether or not this is correct, when a transfusion is considered for the severe anemia and blood-grouping tests are done, it is often found that all prospective donors are incompatible. This is of course due to the presence of a cold agglutinin in high titer with resultant agglutination — at room temperature with the ordinary slide technic — of the red cells of all blood groups. For this reason, transfusions have often been delayed or not given at all in patients desperately needing them. In such an event, the matter is quickly resolved by performing the cross matching at incubator temperature by the test-tube technic described above. I[16] have also recommended in such cases the use of blood that is kept warm from the time of its removal from the donor to its entrance into the blood stream of the recipient.

*For an excellent review of the entire subject of the cold hemagglutinins, the reader is referred to an article by Stats and Wasserman.[12]

The cold hemagglutinin in these cases is also important from the standpoint of chilling of the patient. Thus, marked acrocyanosis and beginning gangrene of the nose, ears and fingertips have been recently described in association with primary atypical pneumonia and a high titer of cold agglutinin.[17] The cold agglutinin may persist for months[15] or perhaps years following an attack of atypical pneumonia, making the person who harbors it liable to the development of hemoglobinuria, chronic hemolytic anemia, extreme coldness and blueness of the extremities or even gangrene on exposure to extreme cold. In a case under study at the present time, all these symptoms have been present since an attack of pneumonia two years ago.[18] Two or three further attacks have occurred in the interim. The cold hemagglutinin is present in a titer of 1:128,000. Because of the presence of a chronic hemolytic anemia with splenomegaly, it is likely that this patient has considerable in vivo autoagglutination, which is enhanced by exposure to cold. Stats and Bullowa[19] report a somewhat similar case in which symmetrical gangrene of the tips of the extremities occurred with exposure to cold. This patient did not have a hemolytic process, but the in vivo agglutination of red cells could be demonstrated by introducing ice water into the conjunctival sacs and examining the bulbar and palpebral conjunctivas with the slit-lamp corneal microscope.

From these and other observations several conclusions may be drawn. First, patients with primary atypical pneumonia should under no circumstances be chilled. Second, if a transfusion becomes necessary because of an acute hemolytic reaction, the cross matching should be done by the test-tube technic at incubator temperature. Third, warm blood should be used and the apparatus, tubing and so forth should be kept constantly as warm as possible. Cold blood withdrawn from the refrigerator should not be used, certainly not before proper warming.

Transfusion Reactions

Severe and often fatal transfusion reactions still occur all too frequently. Exact statistics on their incidence are almost impossible to obtain because most of them go unreported. They are probably as frequent as they are because blood grouping is often relegated to inexperienced persons with little awareness of the great responsibilities involved in correct typing and cross matching. The development of a fatal transfusion reaction in a relatively healthy young person who is being prepared for an elective operation is a tragic event that is in many cases due to omission of either the typing or the cross-matching test. Each transfusion should be preceded by careful cross matching of the recipient's serum with the prospective donor's red-cell suspension and by typing of both the recipient and the prospective donor. Except under very special circumstances, it is not necessary to do the so-called "minor agglutination" — that is, the donor's serum versus the recipient's red cells. If the same blood groups are used, no agglutination with the donor's red cells will occur. If a Group O donor, for example, is used for a Group A recipient, the resultant agglutination with the donor's red cells is to be expected because members of Group O have anti-A and anti-B agglutinins in their serums.

As noted above, cross matching should preferably be done by the test-tube technic at incubator temperature and for at least thirty minutes. This has recently been made an official recommendation of the (British) Medical Research Council.[20] If an unusual emergency exists and thirty minutes seems too long a period to wait, blood plasma should immediately be given.

A transfusion reaction is best treated by its prevention. The intern or technician who performs the test must be acutely aware of the important responsibility involved — literally one of life and death. Even in an emergency, carelessness and too much hurry are inexcusable. Even with all precautions carefully observed, a severe reaction occasionally occurs, that is, the in vivo biologic test is at times more accurate than any form of in vitro testing. For this reason, the recipient should be carefully watched, particularly during the administration of the first 50 to 100 cc. of blood. If there is any complaint whatever of pain in the back or flanks, pain down the legs, a smothering sensation, a burning sensation in the face, a sense of constriction, a chilly sensation or chill or even a sense of something wrong, the transfusion should be immediately discontinued. These symptoms are usually indicative of intravascular agglutination. Whereas the recipient can usually survive the administration of 50 to 100 cc. of incompatible blood, the agglutination of 500 cc. of blood is usually fatal. The investigation of the causes of a severe hemolytic transfusion reaction is described by Mollison.[21]

Red Cells from Bank Blood

The great developments in the use of plasma resulted in almost complete ignoring of the mass of red cells, which were almost routinely discarded. Many observers, however, have remarked on this great waste in a valuable by-product, and in recent publications suggestions for its use have been made. The British workers MacQuaide and Mollison[22] and Williams and Davie[23] used the red cells for the treatment of anemia. Bagdasarov,[1] the director of the Russian Central Institute for Blood Transfusion, reported in 1942 that the red-cell mass was best preserved at 4 to 6°C. with a solution containing magnesium sulfate, potassium chloride and sodium chloride; no marked change in red cells occurred up to twelve days. The red cells were found of great value in cases of severe anemia following blood loss. Watson[24] pointed out that by the use of a thick red-

cell suspension one could rapidly increase the oxygen-carrying capacity of the blood with a minimum of introduced solution. This was particularly useful in ambulatory patients and in certain cardiac patients with anemia. Alt[25] stated that the main value of red-cell transfusions is to increase the erythrocyte count in patients with anemia, particularly following severe hemorrhage. Other suggested uses are in patients with severe iron deficiency and in progressive refractory anemia — that is, in cases with bone-marrow disease due to aplasia, leukemia, tumors and so forth. Because red cells in suspension may be given in concentrated form, larger numbers of them can be given at one time and more frequently than with the use of whole blood. Litwins[26] has suggested the use of Group O red cells admixed with pooled plasma to form a completely universal Group O blood — that is, one containing no agglutinogens and more or less completely neutralized agglutinins.

A new use for preserved red cells — the promotion of normal healing — was suggested by Moorhead and Unger.[27] Seldon and Young[28] state that such red cells either from a single or from different blood groups, when mixed together and stored in a refrigerator for days or weeks, form a gelatinous mass that may be used as a dressing material for wounds, burns, ulcers and chronic infections. This was found of distinct value in the promotion of growth of vascular and connective tissue in the injured surfaces. Because of the difficulty of keeping the semiliquid red-cell material in contact with the wound, Seldon and Young dried it and used it as a fine sterile dusting powder applied directly to the wound surface. Infected wounds, poorly healing postoperative abdominal wounds, certain proctologic cases, varicose and other ulcers of the leg and amputation stumps have been successfully treated. The method seems to offer distinct possibilities in the treatment of healing wounds.

Because of these two developments, the formerly discarded red-cell by-products of the blood bank are now of distinct value; this applies to the treatment of severe anemia, particularly when the regenerative capacity of the bone marrow is impaired, and in the promotion of better wound healing.

Blood Substitutes

Liquid plasma. Liquid plasma when prepared under completely aseptic precautions has been stored at room temperature for a year and a half or longer.[29] During this time, it loses none of its protein or colloidal osmotic value, but there is a rapid loss of antihemorrhagic factors, such as prothrombin, and of complement. Newhouser and Lozner[29] state: "The permissible temperature range of preservation probably lies between 15 and 30°C. (59 and 86°F.). Below this range excessive fibrin precipitation may occur, and above this range protein denaturation occurs rapidly."

The chief advantage of pooled liquid plasma is its ready availability. It may be taken off a shelf and without further testing, reconstituting or other steps be given immediately to a patient in shock. The intravenous set should contain a suitable filter to hold back particles of fibrin. The chief disadvantage of liquid plasma is that it is an excellent culture medium for the growth of bacteria; hence, unless plasma is scrupulously prepared, preserved and tested for sterility, it may well become infected.

Plasma may be given in so-called "units" of 250 cc. each; the recent tendency has been to give larger doses than 1 unit. Thus, 4 units (1000 cc.) may be given without danger, although due consideration should be given to the relatively large amounts of sodium and citrate that are introduced. A caution against the too liberal use of citrated blood was recently voiced.[30] Citrate may be quite toxic, although the toxicity depends to some extent on the rate of injection. Five grams of citrate given intravenously may be considered as a safe maximum, since 15 gm. has been shown to be fatal. Since 50 cc. of a 2.5 per cent solution (1.2 gm.) is customarily used for 1 unit of plasma, this indicates that more than 4 units of plasma, or 1000 cc., should not be used. A citrate reaction[31] which may result in tetany owing to the binding of calcium, is characterized by the development of a positive Chvostek sign, a general tingling sensation, dilatation of the pupils and, finally, actual clonic twitching. The reaction can be quickly terminated by the intravenous injection of calcium chloride or gluconate.

Frozen plasma. Liquid plasma may be preserved in the frozen state in special refrigerators that maintain a constant temperature of −15 to −20°C. Under such conditions, there is indefinite retention of the various thermolabile constituents of the plasma. Reconstitution from the frozen state requires about thirty minutes at a temperature of 37°C., the bottle being placed in a water bath, not an incubator. According to Newhouser and Lozner,[29] the best results in thawing are obtained by this method, followed by maintenance for two to three weeks at room temperature. Quick thawing may be followed by a cloudy plasma.

The chief advantages of frozen plasma lie in the maintenance of sterility and the preservation of immune bodies and antihemorrhagic and other factors. The sterility factor alone has been emphasized as of the greatest importance. The disadvantages of freezing lie in the use of a special, rather expensive freezing unit; the necessity for slow reconstitution (thawing), making it imperative to wait for at least thirty minutes, sometimes a long time in an emergency; and the occasional breakdown of current or apparatus, with consequent thawing. These disadvantages can all be obviated by appropriate measures, some of which are covered by Newhouser and Lozner.

Dried plasma. This material, prepared by dehydrating liquid plasma by one of several processes, can be quickly reconstituted by the addition of pyrogen-free distilled water. It contains in unaltered form both albumin and the various thermolabile globulin constituents of the previously liquid plasma and, what is more, preserves them for many months without appreciable loss of activity. It has a wide range of safety with regard to temperature and bacterial contamination. It should not, however, be allowed to freeze or to stand for any length of time at a temperature above 55°C.[29]

The unusual value of dried plasma in shock and cerebral accidents was quickly recognized: it could be reconstituted in relatively small amounts of fluid, thus obtaining a hypertonic material which would draw unusual amounts of plasma into the circulation and simultaneously dehydrate certain swollen tissues, such as an edematous brain. The use of two-times, four-times and five-times concentrated plasma has been advocated as a routine measure by various investigators. With twice-concentrated plasma, 250 cc. of water can be used to reconstitute the dried material obtained from 500 cc. of plasma. This is probably more effective in shock than is isotonic plasma, and furthermore adds to the circulation at once an adequate amount of protein. Four-times or five-times concentrated plasma possesses the diluting function in even greater fashion than the twice-concentrated material. Erf and Jones[32] dissolve the dry material obtained from 500 cc. of whole blood in 60 cc. of water, which is given by syringe rather than by gravity, as is customary when amounts over 50 or 60 cc. are used. They claim that this is a far quicker and more readily available method, especially for use on the battlefield, than is the gravity-tubing-filter method. Heyl and his collaborators[33] state that the viscosity of concentrated plasma because of the presence of the globulins is much greater than that of concentrated albumin (see below). The total osmotic pressure is furthermore greater because of the presence of concentrated electrolytes; however, the colloid osmotic pressure is less than that of concentrated albumin solutions.

Thus, dried plasma has many advantages: its availability at almost any temperature; its elasticity with reference to the amount of solution that need be added, thus allowing complete control of the degree of desired colloid osmotic pressure; and its retention of sterility under almost any conditions. Its possible disadvantages lie in its use in too highly concentrated form: here if the patient is dehydrated, there may be further drying of various tissues while the blood volume is becoming increased. Furthermore, in a patient with myocardial involvement, the rapid increase in blood volume may impede the circulation.

Dried plasma has its greatest usefulness in shock and related states. It is of value in other conditions as well: in hypoproteinemia, especially with edema, to add protein; in certain conditions of local edema, as in the brain and the extremities, when other methods of therapy have failed; in chronic or acute nephritis as a diuretic, even in the absence of hypoproteinemia; and in severe hepatitis, particularly in the presence of a reduced blood protein and ascites. It would probably be even more widely — and perhaps unwisely — used in civilian practice than it is at present were it less expensive. Sufficient dried plasma for the military services has fortunately been supplied by volunteer donors, with the invaluable assistance of the Red Cross and of various pharmaceutical houses.

Human albumin. Plasma is a highly complex solution. It not only contains proteins that are essential for its own stay in the circulation but has all the various hormones, enzymes, metabolites and so forth that are in process of transportation from one tissue to the others. It has been customary to divide the plasma proteins roughly into two fractions: albumin and globulin. The albumin fraction is relatively pure, but the globulin fraction is composed of a large number of substances that differ greatly from one another with respect to their chemical structure and their function. Although great strides have been made in studying these complex proteins, it is probably safe to say that thus far only the surface has been scratched. Two of the important tools in studying the plasma proteins are the Tiselius apparatus for the observation of electrophoretic mobilities and the ultracentrifuge.

The task of purification and fractionation of human and animal plasmas for military use has been undertaken by the Department of Physical Chemistry at the Harvard Medical School, under the direction of Professor E. J. Cohn. Disregarding respiratory, hormonal and enzymatic proteins, the plasma proteins may be divided according to Cohn,[34] into those concerned with clotting of the blood, with complement, with immune processes, including antibody and antitoxin, and with water and electrolyte balance. Among those that have thus far been identified are fibrinogen and prothrombin and the "mid-piece" and the "end piece" of complement. The bulk of the various globulins comprising the globulin fraction of plasma has thus far not been separated in pure form; they have been characterized either as euglobulins or pseudoglobulins or — in terms of their electrophoretic mobilities — as alpha, beta and gamma globulins. In general, the globulins have an extremely high molecular weight and on that account exert a smaller osmotic pressure than do the smaller molecules of albumin. The separation in relatively pure form of the simpler albumin fraction from the complex globulins has been effectively accomplished by Cohn and his collaborators.[34]

The albumin thus prepared and freed from the more labile and more readily denatured fibrinogen and globulins is readily soluble in water, yielding clear solutions even at concentrations containing as much as 70 per cent of albumin by volume. Even in

concentrated form, albumin solutions have a lower viscosity than has plasma, interact only slightly with other proteins and salts and stand up under conditions of extreme heat and cold.[29] They furthermore exert a much greater colloid osmotic pressure than does whole plasma. For these reasons and because of their immediate availability for intravenous injection, albumin solutions have proved extremely useful in the treatment of wound shock. The standard Army-Navy package of concentrated human-albumin solution consists of 25 gm. of albumin in 100 cc. of buffered salt solution, supplied in a large ampule ready for instant injection by gravity through an ordinary 19-gauge or 20-gauge needle.[29]

Heyl, Gibson and Janeway[33] have calculated that each gram of albumin injected intravenously adds by osmotic pull 18 cc. of fluid to the circulation. These calculations, when subjected to actual experimentation in the human subject, were found to be surprisingly accurate; thus, the actual increment in plasma volume varied from 13.2 to 24.0 cc. in all experiments, with an average value of 17.4 cc. The use of 25 gm. of albumin is thus approximately equivalent to the administration of 450 cc. of normal circulating plasma or 500 cc. of citrated plasma as usually prepared.

Hence, a concentrated solution of purified albumin possesses many advantages. Certain disadvantages must also be assessed. Because of its very great osmotic pull, there is a danger of dehydrating vital tissues, especially in soldiers and others who have been exposed to many hours of struggle under conditions of extreme heat and thirst. For this reason, the use of albumin solutions should probably be restricted to hydrated or only slightly dehydrated persons. Another disadvantage of albumin solution is its lack of globulin substances and thus of enzymes, blood coagulating materials and antibodies. The administration of several injections of albumin solution has furthermore been found to result in a modification of the albumin-globulin pattern of the plasma, with possible effects on immune reactions.[35]

Indications for albumin solution are thus relatively few, and depend entirely on its great colloidal osmotic pull. It is useful in shock and in conditions associated with hypoproteinemia and edema. As yet, it is not available for civilian use; even if it were, its cost would probably render its use almost prohibitive. Partly for this reason and also because of ready availability, the preparation of albumin from animal sources has been given much thought.

Bovine albumin. Cohn and his collaborators[34] have shown that human albumin and bovine albumin present remarkably similar molecular patterns from a physiochemical point of view. Both by means of the ultracentrifuge and the Tiselius electrophoretic apparatus, the two albumins are to all intents and purposes indistinguishable. The chief difficulty, however, is not the physicochemical one but rather the immunologic reaction. This probably develops because of slight contamination of albumin with globulin. The matter of development of sensitivity to a heterologous material is of great importance and has been studied by Janeway[36] and by Heyl, Gibson and Janeway.[33] The latter authors came to the following conclusion: "No statement regarding the safety for intravenous use of crystallized bovine serum albumin of low globulin content can be made until more extensive clinical tests have been completed in order to determine to what extent and under what circumstances it will be safe to use a protein of animal origin for therapy in man."

Sites of Administration of Blood and Blood Substitutes

The preferred site of administration of whole blood, plasma, and the various blood substitutes is naturally in the various large veins, which are usually readily found in the antecubital fossas. In extreme shock and in extensive burns, these veins may either be collapsed or inaccessible. It is well, therefore, in emergencies to have in mind the possibility of administering these substances in other than the basilic veins.

The femoral vein is not customarily thought of in this regard, but its use might well be increased. The vein is extremely large and is situated just medial to the femoral artery, which is readily palpated in the inguinal region. With a little practice, puncture of the vein is readily performed. Administration of plasma by this route was found extremely useful by the Boston City Hospital group during the Cocoanut Grove fire disaster in 1942.

The infusion of blood and other fluids by way of the sternal marrow was suggested by Tocantins[37-39] in 1940 and has gradually assumed increasing value. Tocantins demonstrated by careful injection experiments in cadavers, and later by clinical studies in animals and human beings, that substances injected into the marrow cavity are immediately taken up into the venous circulation apparently unchanged. In adults, the marrow cavity of the sternum is readily entered by the introduction of a sternal-puncture needle — an abbreviated stiff lumbar puncture needle will do — through the skin and subcutaneous tissue and through the anterior lamella of the sternum. The procedure, which is done under novocain anesthesia, is a simple one and is readily learned. A sensation of give is felt when the needle enters the marrow cavity. The stilet is then withdrawn and a small amount of marrow is aspirated. An adapter may be attached to the needle and to rubber tubing and a gravity device, or the blood or fluid may be introduced under positive pressure by means of a syringe. If the injection of more than 50 cc. is contemplated, it is wise to use a two-way stopcock and thus avoid removing the syringe from the needle for each 50 cc. As Tocantins states, rapid injection — over 20 cc. per minute — may be accompanied by a sense of pressure or grinding pain

similar to that of angina pectoris; this quickly disappears at the termination of injection. It is, however, rarely necessary, or even advisable, to inject fluids at such a rapid rate. The use of the intrasternal route is particularly applicable to military medicine, and a number of reports from military establishments in which its use is favorably commented on have appeared.[40, 41] In one such report, the sternal-puncture needle was allowed to remain in situ for three or four days, with occasional cleaning; 14,000 cc. of blood and fluid was given with no untoward effect.

The marrow may also be used for the introduction of fluids and blood into the infant's circulation. Tocantins's studies have shown that in the newborn and in early infancy the marrow cavity either above or below the knees is best utilized. In older children, aged two to four, the mid-tibia may be better. Above the age of four, the sternal cavity is fairly well developed and thus available for injection.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 30171

PRESENTATION OF CASE

A fifty-nine-year-old housewife entered the hospital because of a bearing down sensation in the pelvis.

The patient was in good health until three months before admission, when she noticed "something falling into the vagina" whenever she stood up or walked around. On examining herself she found a small lump in the vagina. These symptoms persisted. She had had no nocturia, vaginal discharge, incontinence, increased frequency or bleeding.

She had had tuberculosis at twenty-nine and passed five years in a sanitarium, at which time she had a phrenectomy. At fifty she had a pulmonary hemorrhage and stayed in bed for two years. She had had a right nephrectomy for renal tuberculosis eight years prior to admission. She had had occasional indigestion over a period of many years without known nausea, vomiting or diarrhea. The menopause occurred at fifty-one.

Physical examination showed a well-developed, obese woman in no distress. There was dullness over the right lung posteriorly and over the left apex, with coarse rales throughout. The heart was normal. Tenderness was elicited over the nephrectomy scar. Pelvic examination showed a rectocele and a cystocele.

The blood pressure was 150 systolic, 75 diastolic. The pulse was 100; the temperature and respirations were normal.

Examination of the blood was normal. The urine was normal. A blood Hinton test was negative.

X-ray examination of the chest showed evidence of inactive tuberculosis in both lungs. An intravenous pyelogram showed a normal left kidney. The right kidney was absent.

On the fourth hospital day a vaginal hysterectomy and a perineal repair were performed. After the first ten minutes there was a fall of blood pressure to 120 systolic, 60 diastolic, and although the patient had a little unusual bleeding, she withstood the operation well. The pathological diagnosis on the uterus was leiomyomas of the uterus and chronic endocervicitis with endocervical polyp. On the second postoperative day the temperature rose to 101°F. She had considerable nausea and belching, without any vomiting. She was given intravenous fluids for two days and 2 gm. of sulfadiazine daily for nine days. The nausea and belching persisted, and the temperature remained at about 100°F. She had some fullness and a questionable mass in the left lower quadrant. On the tenth postoperative day the hemoglobin was 10.7 gm. per 100 cc. An x-ray film of the chest showed no change from the previous examination. On the twelfth hospital day she was propped up and felt very weak and dizzy. She was still quite nauseated and belched a great deal. She began to complain of anorexia and of distress in the left upper quadrant. Examination of the blood on the seventeenth hospital day revealed a red-cell count of 2,180,000, with 6.6 gm. of hemoglobin, and a white-cell count of 11,400, with 71 per cent neutrophils. In the course of the next two days she vomited coffee-grounds material, which was strongly guaiac positive. The prothrombin time was 22 seconds (normal, 22 seconds). She was given several transfusions. The vomiting subsided, and the red-cell count was 2,500,000, with 7.1 gm. of hemoglobin.

A gastrointestinal series on the twenty-second postoperative day showed a hiatus hernia that measured about 9 cm. in diameter (Fig. 1). The mucosa in the hernia and in the adjoining subdiaphragmatic part of the stomach appeared somewhat widened, but no ulcerations were seen. The hernia was observed to change in size and shape. The remainder of the stomach and the duodenum were normal. There was a laminated, calcified gallstone 8 mm. in diameter in the region of the gall bladder. Following the gastrointestinal series, she had several massive gastrointestinal hemorrhages with bright-red blood in the stools and in the vomitus. She was given nineteen transfusions each consisting of 500 cc. of whole blood, and large amounts of intravenous fluids. She continued to bleed, however, and died on the twenty-ninth postoperative day.

DIFFERENTIAL DIAGNOSIS

DR. ARLIE V. BOCK: It would be interesting to know what the blood findings were. Was the hemoglobin done at the time of the first blood examination?

DR. BENJAMIN CASTLEMAN: It is not recorded.

DR. BOCK: I should like to know whether any stools were examined to indicate whether she was losing blood.

DR. CASTLEMAN: If so, they are not recorded.

DR. BOCK: To go over this briefly, I should say that, in view of the subsequent events, the pelvic condition and the operative procedure probably had nothing to do with the major underlying cause of death. She had a long history of tuberculosis. I

*On leave of absence.

presume that diagnosis is correct in view of the time she was observed in a hospital. The fact that after some twenty years of good health she had a recurrence of the tuberculosis, as indicated by the pulmonary hemorrhage and presumably other signs that are not mentioned, and the fact that she had a nephrectomy, presumably indicate that the diagnosis of tuberculosis had been carefully gone into before the latter step was taken. So I think we can dismiss the problem of tuberculosis in this case. Some amyloidosis might be found, but I do not believe it could be extensive in this well-nourished woman, and I do not know that it could have had anything to do with hemorrhage anyway.

What are the causes of this type of extraordinary hemorrhage, so severe as to cause death and coming on following the operative procedure that I said I doubted had anything to do with the underlying trouble? The first and obvious thing is the description of the hiatus hernia. The history of bleeding given here, if it has anything to do with hiatus hernia, is decidedly atypical. We know that the usual type of bleeding is oozing for weeks or months, with the development of a secondary anemia, and then subsiding, with gradual recovery from the anemia. Then a secondary period of oozing starts and secondary anemia again develops. The history is usually quite silent. A gastrointestinal disorder with such a hernia usually is infrequent, but when it does occur is characteristic, with a story of difficulty with swallowing or trouble when in the upright position, often relieved by lying down. If the patient bends over, especially to the left, there may be a sensation of something being squeezed up into the chest. There are usually odd sensations of that kind, none of which were present in this case.

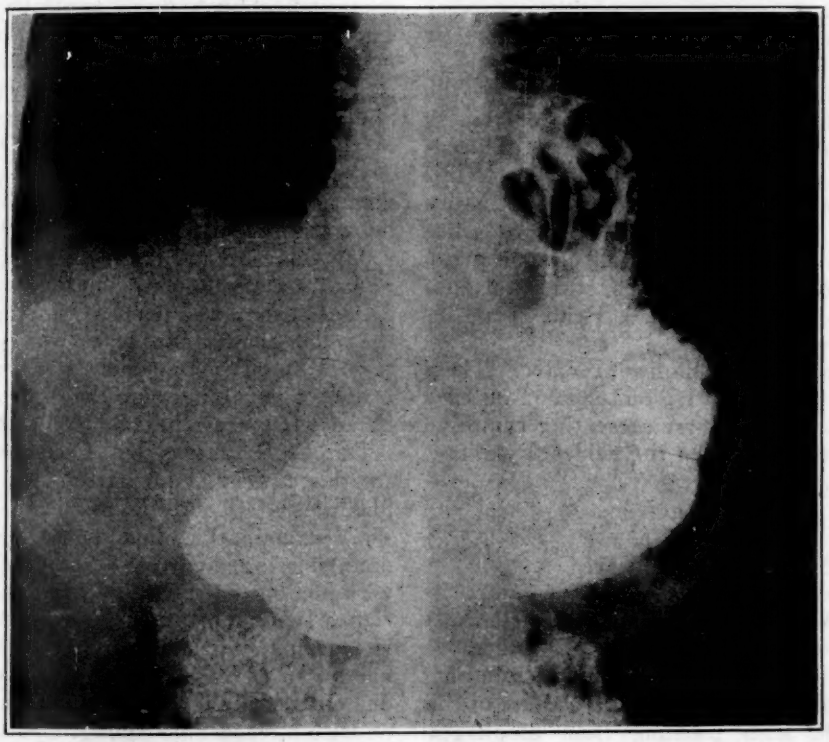

FIGURE 1. *Roentgenogram Showing the Hiatus Hernia.*

The indigestion that is mentioned may very well have been due to the presence of cholecystitis and stone.

May I see the x-ray films?

DR. MILFORD SCHULZ: These films merely demonstrate what has already been said in the protocol. Here we have the large hiatus hernia, an unusually large one; apparently it is not paraesophageal, from what can be seen here. There is no evidence of a lesion elsewhere in the stomach or duodenum.

DR. BOCK: In this hospital we have seen many cases of hernia of the stomach much larger than this one.

I should have supposed that if the bleeding in this case were due to hernia, there would have been more history of indigestion, more suggestion of secondary gastritis and much more history of bleeding with a resultant anemia, which would have announced it-

self to the patient by fatigue, palpitation and all the things that go with such an anemia. In view of the fact that the history is silent with reference to this hernia, I am inclined to rule it out as the cause of the bleeding. It is certain that some of these patients have massive hemorrhages and even bleed to death. I suppose that the mechanism of such bleeding is increased venous pressure in the part of the stomach above the diaphragm. There are no ulcerations of the mucosa that bleed. At post-mortem examination this part of the stomach is quite red from congestion, and the part below the stricture pale and normal. But in the present case, with this type of massive bleeding and a silent history, I doubt that the bleeding came from the hiatus hernia.

The next thing that one should consider is the presence of a peptic ulcer. If one rules out hiatus hernia and associated gastritis as the cause of bleeding, then ulcer is the next commonest cause of this type of bleeding, but there is nothing in the history to suggest it. That may not be important, since hemorrhage is often the first sign of ulcer in many cases. I am also influenced by the fact that the duodenal cap is described as normal. Hence, I am inclined to rule out ulcer.

Another possibility is cirrhosis of the liver. There is no history to suggest it; but, again, massive hemorrhage may be the first presenting symptom of cirrhosis of the liver. On the evidence we have here, I cannot rule it out.

Was the serum protein done?

DR. GORDON DONALDSON: No.

DR. BOCK: The dye retention test?

DR. DONALDSON: No.

DR. BOCK: We have no evidence either clinically or from the laboratory data to confirm the diagnosis of cirrhosis, and yet I think it cannot be ruled out and I have to consider it seriously as a cause of this woman's death, with bleeding from esophageal varices.

Did she have a nonvisualized leiomyoma of the stomach? We have made mistakes in the past, when we found nothing by x-ray examination, in assuming that bleeding of an extensive sort in the gastrointestinal tract was due to the presence of an unvisualized ulcer. That is a serious mistake, and because leiomyoma may be present, we should not be satisfied to treat a patient who is bleeding and has had bleeding on a number of occasions by assuming that the diagnosis is one of peptic ulcer. A leiomyoma may be responsible for severe hemorrhage and may cause repeated hemorrhages before anything positive is found by x-ray examination. We have nothing here to support such a diagnosis except the history of hemorrhage.

Judging from the cases of hiatus hernia that I have seen I am inclined to rule this lesion out as the cause of bleeding. I do not believe that the patient had an ulcer. I think that the diagnosis is cirrhosis of the liver or, less likely, leiomyoma. Amyloid disease may have been found. Without a gastroscopic examination, there is nothing to help in the diagnosis of gastritis.

DR. LELAND S. MCKITTRICK: Does the bright blood that she passed by rectum bother you at all, Dr. Bock, in accepting a lesion of the stomach or esophagus as the source of the bleeding?

DR. BOCK: It does not say how much, but I believe the hemorrhage was considerable and came very rapidly; I still think it was a high hemorrhage.

DR. DONALDSON: Preoperatively, we directed all our efforts toward ruling out tuberculosis as a contraindication to doing anything to the prolapse. The chest and kidney situation was evaluated, and I must say that it was not until after she had bled postoperatively that we got a story of indigestion. She said she had had indigestion only when she was in the tuberculosis sanitarium. On bed rest, she developed indigestion, but never had any nausea or vomiting. We did not discover that she was bleeding until the eighth postoperative day, when we propped her up and found that she was dizzy. She was a fat and sallow woman, and we did not appreciate that she was anemic. On rechecking, we found that the hemoglobin level was surprisingly low, several stools were guaiac positive. We perhaps made a mistake in doing the gastrointestinal series, because following that she bled profusely.

DR. MCKITTRICK: Dr. Donaldson asked me to see this patient in Dr. Arthur W. Allen's absence. She presented quite a problem. Concerning the x-ray examination that Dr. Donaldson tends to doubt his judgment on, I should like to take issue with him on that point, because I think that he was right. It is important to know from where a patient is bleeding, particularly if there is a question of operation. If a definite ulcer could have been demonstrated, this woman would have been operated on with a reasonable chance of surviving the operation. The absence of a demonstrable ulcer, which, as Dr. Bock has said, does not exclude it, makes it less likely and possibly changes the method of approach. So I feel that an x-ray is worth the risk that it may incur in unexplained gastroduodenal bleeding.

Of course the problem was to control the bleeding. The patient had bled massively, or at least she lost a lot of blood. It came from the gastroduodenal region. We thought that it probably did not come from a duodenal ulcer. The bleeding was more massive than that which occurs from hiatus hernia; but knowing that massive bleeding occasionally does arise from that source, we thought that that was probably the answer and we treated her on that basis.

I felt much disturbed about this patient, and I thought that I had let down both Dr. Donaldson and Dr. Allen in not having advised operation. There was one thing in the history that I should have paid more attention to. When a patient bleeds

as massively as this patient did we have a right on a clinical basis to assume that the bleeding is coming from a large artery. It would be unusual for a diffuse process such as one ordinarily associates with a hiatus hernia to bleed a patient out as promptly as this patient did bleed out. That is rather characteristic of bleeding from a large single vessel, such as occurs in a posterior duodenal ulcer. Therefore, it seemed to me, after this patient had got to the point where we could not operate on her, that I had "missed the boat," in that she probably had a fairly active ulceration of a vessel that might have been amenable to surgical attack. By the time I had convinced myself that that might have been the answer, it was too late to do anything about it. She was not a good operative risk. If we had operated, and if she had nothing that we could get at directly, she probably would never have got off the table.

Dr. Bock: I think that Dr. McKittrick's reasoning is good, but a patient can have massive hemorrhage and bleed to death from hiatus hernia with a secondary gastritis. Ordinarily one finds oozing of blood from this lesion, with repeatedly positive stools; the patient usually recovers, even though nothing is done about it.

Dr. McKittrick: If I had known of patients dying under the circumstances that you describe, I should probably have felt differently than I did.

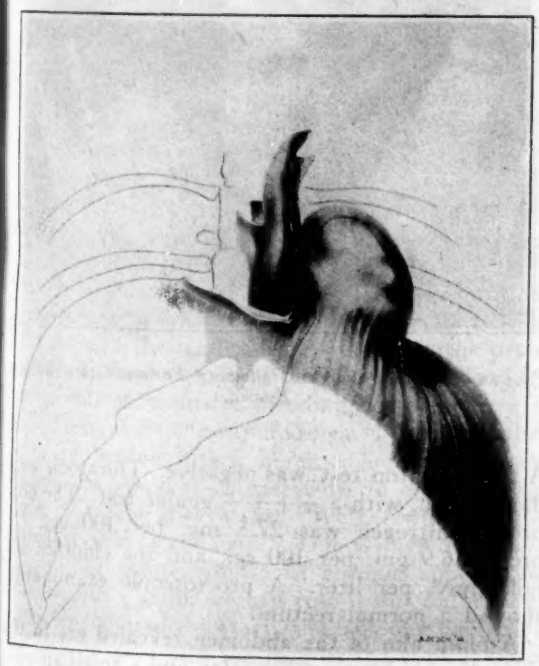

Figure 2. *Drawing of the Hiatus Hernia in Situ.*

On the law of chance, a rapid depletion must be more frequent from a single vessel than from the type of thing that you are talking about, and sometimes one has to gamble on what is likeliest.

Dr. Bock: I think that you are correct. I* first became interested in this problem in 1928, when my first case was explored because I could not believe that the bleeding was due to hiatus hernia. The second case had already been explored by the late

Figure 3. *Drawing of the Interior of the Herniated Portion of the Stomach Showing the Large Ulcer with the Bleeding Vessel.*

Dr. Daniel F. Jones, who would not believe that the bleeding was due to a hiatus hernia, but we later proved that such was the case.

Dr. Castleman: But ordinarily one finds that the bleeding has occurred over a long period of time?

Dr. Bock: Yes; and usually there is a silent history. I cannot believe that this patient bled from the hiatus hernia.

Clinical Diagnoses

Hiatus hernia.

Gastritis, with massive hemorrhage.

Dr. Bock's Diagnoses

Cirrhosis of liver, with bleeding from esophageal varices?

Leiomyoma of stomach?

Old pulmonary tuberculosis.

Anatomical Diagnoses

Diaphragmatic hiatus hernia, with bleeding from ulcer of herniated portion of stomach.

Operation: vaginal hysterectomy and repair, recent; right nephrectomy, old.

Pulmonary tuberculosis, bilateral, inactive.

*Bock, A. V., Dulin, J. W., and Brooke, P. A. Diaphragmatic hernia and secondary anemia; ten cases. *New Eng. J. Med.* 209:615-625, 1933.

Pathological Discussion

Dr. Castleman: The autopsy showed a definite hiatus hernia (Fig. 2). The hernial sac was made up only of pleura and peritoneum, there being no diaphragmatic muscle in that region. The portion of the stomach that was present within the hernia contained a shallow ulcer measuring 4 by 3 cm. (Fig. 3). In its center was an eroded artery, which was the source of the bleeding. We were able to follow that artery back to the gastric artery, which arose from the celiac axis. Microscopic study of the ulcer showed that it did not have the fibrinoid base of a peptic ulcer, but that it was simply necrosis of the mucosa and muscularis mucosa, with a granulation-tissue base. Although the portion of the stomach within the hernia was easily reduced at autopsy, it must have been partially constricted for some time. There was a moderately severe gastritis around the ulcer.

Dr. McKittrick: Do you think that the lesion could have been recognized at exploration?

Dr. Castleman: I believe that the hernia could have been reduced at operation, following which you certainly would have been able to feel the ulcer and probably the pouting bleeding vessel, such as you do in dealing with a posterior duodenal ulcer.

CASE 30172

Presentation of Case

A twenty-three-year-old man was admitted to the hospital because of rectal bleeding.

The patient was in excellent health until about twenty months before admission, when he had severe diarrhea lasting four or five days and consisting of ten or more stools a day. There was intermittent, crampy, generalized abdominal pain, especially on the right. The diarrhea subsided except for two episodes, each lasting for one week and occurring three and ten months after the first attack. The crampy pain was present before, during and after the attacks. Ten months before admission he enlisted in the Army, where he underwent basic training for two months. He then had another attack of crampy, low abdominal pain and diarrhea, for which he was hospitalized. With a bland diet the diarrhea subsided but the pain persisted. A gastrointestinal series and Graham test were negative. A barium enema showed a constricting lesion of the right colon. X-ray films of the chest, examination of the sputum and gastric washings for tubercle bacilli and a tuberculin test were negative. Operation was advised, but he requested, and was granted, medical discharge. Following discharge his condition remained the same. One week before admission he had a small gush of bright-red blood following an otherwise normal bowel movement. He had had no chills, fever, nausea, vomiting, night sweats, loss of appetite or change in weight. No other gastrointestinal or genitourinary symptoms were noted.

Physical examination showed a well-developed, well-nourished man in no distress. The heart and lungs were normal. An abdominal mass was palpated on the right side by one or two examiners. There was no tenderness or spasm.

The blood pressure was 110 systolic, 78 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 5,760,000, with 86 per cent hemoglobin. The white-cell count was 12,500. The urine was normal.

Figure 1. *Roentgenogram following Postevacuation Barium Enema.*

A blood Hinton test was negative. The stools were dark brown, with a ++++ guaiac test. The non-protein nitrogen was 27.5 mg. per 100 cc., the protein 6.9 gm. per 100 cc., and the chloride 102 milliequiv. per liter. A proctoscopic examination showed a normal rectum.

A plain film of the abdomen revealed gas in the ascending and transverse colon and a small amount of gas and feces in the descending colon, but no gas in the rectum. An intravenous pyelogram was negative. A barium enema showed ready filling of the descending and transverse colon up to the hepatic flexure, at which point the bowel was markedly narrowed for 10 cm. (Fig. 1). Proximal to this, the

cecum did not fill easily. The wall was irregular, but without any change in the mucosal pattern except for shelf formation and small ulcerations. The chest films were negative. A Miller–Abbott tube was passed into the small intestine.

On the tenth hospital day an operation was performed.

Differential Diagnosis

Dr. Charles G. Mixter: I think that, at once, one comes to the conclusion from the history of crampy, generalized, abdominal pain, the change in his bowel function, the blood by rectum, and the presence of a probable mass in the right side of the abdomen, as well as the x-ray findings, that we are dealing with a gastrointestinal lesion probably of the large intestine, but possibly of the small intestine.

May we see the x-ray films?

Dr. Laurence L. Robbins: This is the lesion, approximately 8 cm. in length, in the ascending colon extending nearly to the hepatic flexure. The lumen appears to be narrowed to about 2 or 3 mm. in diameter — perhaps 5 mm. at its widest portion. I do not believe that one can be absolutely sure of ulceration, but certainly the possibility is suggested. One thing that does appear to me more significant than is expressed in the report is that the margins are not typically "shelf-like" and seem to change the least bit in the various films. There is absence of the normal mucosal pattern. The chest is negative.

Dr. Mixter: That does not correspond with the usual spool-like type that one would associate with cancer of an obstructive nature.

Dr. Robbins: Not typically.

Dr. Mixter: From these findings we can rule out the other systems, and limit our consideration to the intestinal tract.

As I read this over, there came to mind, of course, the different lesions that I associate readily with three of the factors here — namely, the probable mass, the presence of blood, substantiated by one episode of bright-red bleeding and the ++++ guaiac test, and the x-ray findings. I can remember years ago as an intern here, when Dr. Maurice Richardson would see a case with an obscure diagnosis, he would always say, "Well, I will take the appendix against the field." One always does have to consider the possibility of chronic appendiceal abscess, but I think we can rule it out on account of the duration of the story, the lack of emaciation, the lack of fever and the lack of the typical onset with the attack, and perhaps the presence of diarrhea.

Actinomycosis perhaps would come to mind from the presence of a mass, but again, if the story is as long as the protocol tells us, one would expect the patient to have a frank abscess by this time. Furthermore, in my experience, blood is not a feature in dealing with actinomycosis of the cecum.

Sarcomatous lesions, of course, are more frequent in the small than in the large bowel, and the pressure defect is lateral in type, not the annular type that these x-ray films suggest. The patient could have had bleeding from ulceration, but he was in good physical condition, had a surprisingly good red-cell count, and his white-cell count was only slightly elevated. I think that we can rule out sarcomatous lesions, particularly the lymphoblastic group.

Occasionally one sees a rare case of simple ulceration of the colon. We have had two or three such cases in our clinic at the Beth Israel Hospital. They are generally seen in the older age group, patients who are around fifty or more, and are characterized by bleeding, and by the presence of an ulcer, generally of good size, picked up by x-ray examination. What the etiology is, I do not know. We have not seen them in the perforated stage. Here we find a definitely long, tubular, constricting lesion, so we can rule out simple ulceration of the colon.

Diverticulitis, of course, will cause a constriction and a mass. Diverticulitis is a disease of the old-age group. It is usually, however, not characterized by bleeding. It is almost invariably multiple, and it is much more prone to involve the left colon than the right. The chances are, from all these facts, that we can discard that as a possibility.

Ileocecal tuberculosis is a possibility. Here, in the East, where the majority of milk is pasteurized, the surgical tuberculous lesions of childhood are rare. They have disappeared remarkably in the last thirty years or so. Another large entity that was frequently placed in the group of ileocecal tuberculosis has been removed from that category by the recognition of regional enteritis, or terminal ileitis. Ileocecal tuberculosis, however, unquestionably occurs. Sometimes tubercle bacilli can be picked up in the stools. In the last case that I personally encountered, there was marked involvement of the appendix, which resembled a good-sized yellow banana. That patient had tubercle bacilli that were readily identified in the stool. Usually, of course, there are accompanying signs — evidence of calcareous nodes elsewhere in the abdomen or signs in the chest. It is frequently accompanied by quite severe bleeding and usually by tenesmus. This man was in good physical condition and had no anemia, and I should say that his general condition did not fit the picture of ileocecal tuberculosis.

The patient was twenty-three years old, and because of that, at first glance, one rules out cancer of the ascending colon. Of course that does not always hold. We have had four or five cases of intestinal neoplasm in the twenty-year-old group. One boy that we had a couple of years ago came in with a mass and had a distinct family history of carcinoma, and his father had died less than five years before of carcinoma of the rectum. He had car-

cinoma of the rectum and a diffuse polyposis. At the time of excision we did an abdominoperineal resection and took out the greater part of the sigmoid as well. It showed four degenerative polyps that were definitely carcinomatous. Later we resected the whole colon. Nevertheless, he died of his disease within some three years. So we cannot rule out carcinoma simply on the age. What does he not show that he ought to have to fit the diagnosis of carcinoma? In the first place I think that it is unusual for a carcinoma of the colon to be 8 cm. long. I do not know what the radiographic interpretation would be, Dr. Robbins, but would you not say that that was a long lesion for carcinoma?

DR. ROBBINS: I think that is true anywhere except in the ascending colon, where some of the lesions are extensive. I have seen carcinomatous lesions much longer than 8 cm.

DR. MIXTER: Of course a carcinoma of the ascending colon is usually a lateral-wall lesion that tends to bleed readily and is the cause of marked anemia. A lesion that is associated more truly with the hepatic flexure is annular, and our experience has been that a carcinoma as long as this is out of the ordinary. Certainly I believe that that type of growth is not characteristic of what I should expect with a true annular lesion of the colon. As Dr. Robbins says, it cannot be ruled out, but it would be a little unusual for a patient to have a cancer of that size that had been going on one year and eight months. I should not expect him to have a red-cell count of 5,700,000 with 86 per cent hemoglobin. Furthermore, there was no evidence of malnutrition or cachexia. I think that it is very unlikely that we are dealing with a carcinoma.

It boils down then to other lesions that we should have in mind. The first is ulcerative colitis, and the second is perhaps its first cousin — regional enteritis. Where the dividing line comes is hard to say. It is anybody's guess. The etiology of both diseases is unknown, and they certainly merge one into the other. With ulcerative colitis there may be a backwash infection into the terminal ileum, and we know certainly that regional enteritis may involve the colon — that is, involvement of the ascending colon or skip or contact areas in the sigmoid. It is true that in regional ileitis the frank exhibition of blood is fairly rare, but we have had a definite small group of such cases in our series, and the presence of blood does not, by any means, rule it out. The story is a bit suggestive of regional enteritis. The chronicity, the changes in bowel habit, with diarrhea and intermittent, generalized, crampy pain, and the presence of a mass all fit in with the later stages of the disease.

Before I touch on regional enteritis any further I should like to say that we recognize ulcerative colitis as a disease commonly encountered in the left and not the right colon. Apparently it is prone to start on the left side, and is usually picked up by proctoscopic or sigmoidoscopic examination. Here we have the evidence of a normal proctoscopic examination of the rectum, and I judge that the anal canal was also normal. In other words we cannot explain the bleeding on the basis of a hemorrhoidal gush. Certainly we cannot explain it by an ulceration of the rectum or of the lower sigmoid. Frank bleeding is not particularly uncommon in ulcerative colitis, but the lesion is rare on the right side — perhaps 10 per cent or less originate in the right colon. It is also rare to get an isolated lesion such as this with only slight evidence of involvement in the rest of the right colon, but it would be extremely difficult to rule out completely that diagnosis. I recall a case that I had only three or four months ago — a woman in the early thirties who had a diagnosis made by x-ray of splenic-flexure obstruction probably due to carcinoma. At operation she had a mass that clinically suggested carcinoma, involved the perirenal capsule, and was firmly adherent to the left kidney. On the basis of both the clinical and radiographic evidence, we thought that it probably was carcinoma, and I resected the splenic flexure and the left kidney. On pathological examination it was proved to be a localized area of ulcerative colitis. The thing that gave the show away, so to speak, clinically was the fact that when the resection was done I inspected the descending colon and saw ulcers in the descending colon that were not visible by sigmoidoscopic examination. How far they extended I do not know, but certainly, to the limit of the specimen — 10 or 12 cm. — ulcers were still present. Thus there may be isolated areas of inflammatory reaction that simulate carcinoma but that are essentially a localized lesion. Therefore it would be extremely difficult, to my mind, to rule that diagnosis out.

I believe that this patient had regional enteritis. We recognize four clinical stages of the disease. The first is one of intra-abdominal irritation or inflammation. The second stage, one of ulceration, in which the ulcers tend to be laid down along the mesenteric border, is accompanied by diarrhea, often mucus and occasionally blood, and simulates in its symptomatology an ulcerative colitis. The third stage, that of obstruction, corresponds to the type of disease presented by this patient but which usually, of course, originates in the terminal ileum. It may, however, be low in the large bowel. We have had several cases limited to the large bowel, in which pseudopolyposis of the mucosa and obstructive symptoms became definitely manifest. The fourth stage is that of fistula and abscess formation. The disease, of course, is prone to fistula formation. Our statistics show that well over one third of our patients have fistula or abscess. The sinus frequently forms in previous laparotomy wounds, often in the incision of an appendectomy, which has not cured the disease. It may frequently pass blindly into the mesentery and form an abscess.

It may pass to the cecum, or it may adhere and form a fistula to the sigmoid or into the bladder. We have had several cases in which a fistula formed in the perineum or by passing out the sacrosciatic notch and pointing behind the trochanter of the femur on either side. One patient several years ago came in with five different fistulas, including one in the groin and one in the gluteal region.

My diagnosis is regional enteritis, with probable involvement of the terminal ileum, although there is no good evidence to substantiate the latter, except that, on the law of chances, this might have been a spill-over from a terminal ileum infection that had progressed and localized in the ascending colon. It may have been ulcerative colitis, but my first choice is regional enteritis.

Clinical Diagnosis

Carcinoma of right colon?
Inflammatory obstruction of right colon?

Dr. Mixter's Diagnoses

Regional enteritis of colon.
Terminal ileitis.

Anatomical Diagnosis

Regional enteritis of ascending colon.

Pathological Discussion

Dr. Benjamin Castleman: The specimen we received was a large resection of the right colon and the terminal ileum. About 7 cm. from the ileocecal valve the ascending colon, for a distance of 7 cm., was markedly narrowed and thickened. The mucosal surface was irregular, and there were numerous shallow ulcers with a few mucosal pseudopolyps. Grossly this lesion could be either ulcerative colitis or regional enteritis.

I personally believe that these two diseases are first cousins, as Dr. Mixter suggested. When regional enteritis involves the colon it should look like an ulcerative colitis grossly. Since the small bowel is thinner and more mobile, one does not expect it to respond to an inflammatory reaction in the same way that the colon does. In the cases of regional enteritis involving the colon that we have seen the colonic lesion in the gross looks like ulcerative colitis, so I do not believe that one can tell on gross inspection which disease it is.

Microscopic sections showed a subacute and chronic process with a cellular infiltration of eosinophils, polymorphonuclears, lymphocytes and mononuclears — findings seen both in ulcerative colitis and in regional enteritis. The only possible differential clue that the morphologist has is to find tuberclelike lesions with giant cells in the mucosa or wall of the bowel; these are found in about half the cases of regional enteritis and are almost never found in ulcerative colitis, although we have seen them in two cases of diffuse ulcerative colitis. This case did show a few tuberclelike lesions with giant cells, so that I am more inclined to believe that the lesion was regional enteritis of the colon rather than right-sided isolated ulcerative colitis. It certainly was not tuberculosis.

Dr. Mixter: Were there lesions in the terminal segment of ileum?

Dr. Castleman: No.

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POPULATION PROBLEMS

PROFESSOR KARL SAX* has recently presented some interesting facts concerning the population problems that are confronting us, and that will have to be solved before a more abundant life and freedom from want can be guaranteed to the peoples of all nations, by any individual or group of individuals. Such promises seem to have been made with no regard to agricultural production or to population pressure.

Statistics are available that give point to our doubts concerning the economic and political largesse that we are so eager to scatter. Man, for instance, had been present on the earth for five hundred centuries before the population reached 850,000,000 people; in one additional century this population had doubled, and at the present rate of increase the population of today, which is over two billion, will again nearly double before the end of this century. Two and a half acres of arable land are needed to support each person — that is, to provide him with essential food, clothing and other necessities. Improved agricultural methods and a lower standard of living may cut this down somewhat, but not greatly, for although parts of the population of Asia subsist on less than an acre per head, they live at a bare survival level. Certain enthusiastic publicists, even scientists, have predicted that when the synthesis of food goes into high gear we shall have enough for a population thousands or even millions of times that which exists at present. They forget that an increase of a million times would give each individual something less than a square foot to live on. In comparison to this the top of St. Simeon's pillar would seem like a farm in the country.

Under the present world economic system — or lack of it — practically none of the nations of Europe except Russia are able to produce enough food to maintain adequate nutritional standards. In Asia, millions of acres have been exhausted by continued cultivation and erosion, and no new fertile areas are available for exploitation. In this country, even with intensive, scientific cultivation, we are little more than maintaining crop yields at a stationary level, and are using up our arable lands faster than we are restoring them.

Three methods, according to Dr. Sax, have been followed in the overcrowded nations of Europe when population pressure exceeds the food supply: industrialization and the importation of foodstuffs in exchange for manufactured goods; migrations of surplus populations to the newly opened regions of the Americas, Australia and Africa; and the artificial reduction of the birth rate. The first two methods have been practically eliminated by the utilization of most of the available lands, and the only alternative to control of populations that seems to remain open is the intolerable one that we have seen practiced in recent years — invasion of neighboring countries with the gradual extermination of their populations.

*Sax, K. Population problems of new world order. *Scientific Monthly* 58:66-71, 1944.

Mankind has propagated itself into a first-class impasse, and fine words, expansive promises and scholastic arguments are not going to provide the solution. Our world planners will have to do some clever and sage thinking if they are going to make a postwar world tick properly in all its various parts.

FOR THE WELFARE OF MANKIND

On October 17, 1943, the Commonwealth Fund completed its twenty-fifth year. It was founded in 1918 by Mrs. Stephen V. Harkness, with the simple instruction "to do something for the welfare of mankind." Thus conceived without legal impediments or inhibitions, such as too frequently fetter the generosity of an otherwise worthy and enlightened donor, this foundation has now firmly established itself as an outstanding American institution.

During the past quarter century the Commonwealth Fund has given away some $41,000,000, which is in itself a great accomplishment. Its first grant was for war service, and the distress of Europe and of the Near East dominated its giving for the first two years. There next developed a major swing toward the problem of mental health, and then an expanding interest in public health, hospitals, medical education and medical research. These are the fields to which the Fund has increasingly devoted itself and in which it has become so well known to the medical profession. Another steadily developing and large interest has been that of international fellowships; these are now being adjusted to world conditions by the awarding of appointments in increasing volume to students and scientists from the other nations of the American hemisphere.

Among its many medical influences the Fund has perhaps come closest to the physician in its study of the "rural hospital." The American Medical Association and the American College of Surgeons have shown great interest in hospital standards but have never paid much attention to the problems arising in the small hospital. These have been the concern of one of the larger divisions of the Commonwealth Fund for an extended period, and the educational opportunities presented by the small hospital have been exposed and explored, which has proved to be a distinct contribution to medical education. The Division of Publications is likewise noteworthy for its printing of material that might not otherwise have been recorded. The fact that such printing does not have to meet the criteria of commercial success has given some of it a peculiar value in the fields covered. The Division of Public Health and the Division of Health Studies have likewise had a helpful influence on the evolution of social attitudes toward health.

Beyond all this the Fund has been fortunate in being able to avoid great and long-term commitments while it felt the pulses of war and peace, of science and education and of public health and medical research. On this account it has developed a concept of philanthropy that is maturing, much as a person, with the experiences of the passing years. It freely states that it has made mistakes, yet "there has been a trend of continuity in its giving and, it is hoped, some progress in learning how to give." The *Twenty-Fifth Annual Report* of the Commonwealth Fund reveals an institution of modesty, freedom and vigor —a significant combination in professional philanthropy.

MEDICAL EPONYM

The Cushing Suture

The Cushing intestinal suture is often wrongly attributed to Dr. Harvey Cushing. The description of this suture was written by Dr. Hayward W. Cushing (1854–1934) and appears on page 83 of *Medical and Surgical Reports of the City Hospital* (Boston, 1889). The article is entitled "The 'Right Angle' Continuous Intestinal Suture." Dr. Cushing was one of the members of the surgical staff of the Boston City Hospital, headed at that time by Dr. David W. Cheever. After discussing and classifying intestinal sutures then in use, he describes the new suture as follows:

> A short experience with the above-mentioned types demonstrates that the "Continuous" sutures have a great advantage in regard to the ease and rapidity with which they can be inserted. The time spent in knotting a fine wet thread, with fingers sticky with blood, in an intestine which is more difficult to handle than a wet rag, is surprisingly long. . . .
>
> A resected intestine is united by the suture . . . as follows: It is begun at one side of the mesenteric attachment by an inverted Lembert suture, which is tied, and the free end left pendent from the knot. The resected edges are now united by the "Right Angle" suture . . . commencing at the point of union already made . . . and continued along parallel to the resected edges of the gut, till the free end, at the point of commencement, is reached.

F. D. M.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

COBURN — Clarence O. Coburn, M.D., of Candia, died March 30. He was in his sixty-second year.

Dr. Coburn, son of William P. and Sarah (Hubbard) Coburn, was born in Manchester and graduated from Tufts College Medical School in 1906. He was vice-president of the Manchester Rotary Club, a trustee for several years of the Currier Gallery of Arts, president of the Medical Staff at the Elliott Hospital and a member of the Manchester, Hillsborough County and New Hampshire medical societies. He served as president of the New Hampshire Medical Society in 1939.

He is survived by his widow, two daughters, one son, four brothers and one sister.

NOTICES

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston

Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Wednesday, May 3 — Harmful Effects of Recumbency in the Treatment of Heart Failure. Dr. Samuel Levine.

Friday, May 5 — Errors in Cardiovascular Diagnosis. Dr. Paul D. White.

Wednesday, May 10 — Electric Shock Treatment. Dr. Abraham Myerson.

Friday, May 12 — The Value of Nephrostomy. Dr. Roger Graves.

Wednesday, May 17 — Some Clinical Aspects of Coccidioidomycosis. Dr. Norman Culiner.

Friday, May 19 — Diagnosis of Pancreatic Disease. Dr. Joseph H. Pratt.

Wednesday, May 24 — Prefrontal Lobectomy Indications and Results. Dr. Kurt Goldstein.

Friday, May 26 — Clinicopathological Conference. Drs. David Ayman and H. E. MacMahon.

On Tuesday and Thursday mornings Dr. S. J. Thannhauser will give medical clinics on hospital cases.

On Monday mornings clinics will be given by Dr. Samuel Proger. On Saturday mornings clinics will be given by Dr. William Dameshek.

BOSTON CITY HOSPITAL ALUMNI ASSOCIATION

There will be a clinical meeting of the Boston City Hospital Alumni Association on Saturday, May 6, in the Cheever Amphitheater, Dowling Building.

PROGRAM

Sternal Puncture Therapy. Dr. Henry Baker.

Treatment of Hydrocephalus in Cephalic Presentation (with motion pictures). Dr. Arthur J. Gorma.

Fluoroscopic Method of Nailing Hips and the Results (with motion pictures). Dr. Newton C. Browder.

Prevention and Treatment of Pulmonary Embolism (with lantern slides). Dr. Everett E. O'Neil.

Penicillin. Dr. Chester S. Keefer.

Luncheon for the alumni, as guests of the trustees, will be held in the House Officers' Dining Room at 12:30 o'clock.

WASHINGTONIAN HOSPITAL

Mr. Reuben L. Lurie, chairman of the Parole Board, Massachusetts Department of Correction, will give the final lecture in the series on alcoholism, being held under the cosponsorship of the Washingtonian Hospital and the Committee on Alcoholism of the Boston Council of Social Agencies on Friday evening, May 12, at 7:30, at Zero Marlborough Street, Boston. His topic will be "Alcoholism, Criminology and Parole." Mr. Elwood H. Hettrick, dean of the Boston University Law School and a member of the Board of Directors of the hospital will preside.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, May 4, in the classroom of the Nurses' Residence at 7:15 p.m. Dr. Susannah Friedman will present and discuss the following two cases from the Urological Department: "Multiple Bilateral Renal and Ureteral Calculi and Their Removal" and "Bladder Papillomas — Late Complications."

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 4

THURSDAY, MAY 4

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

7:15 p.m. New England Hospital for Women and Children. Monthly clinical conference and meeting of the staff.

FRIDAY, MAY 5

*9:00–10:00 a.m. Errors in Cardiovascular Diagnosis. Dr. Paul D. White. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Massachusetts Central Health Council. The Pioneer, Y. W. C. A., 140 Clarendon Street, Boston.

SATURDAY, MAY 6

*9:00–10:00 a.m. Medical clinic. Dr. William Dameshek. Joseph H. Pratt Diagnostic Hospital.

12:30 p.m. Boston City Hospital Alumni Association. Cheever Amphitheater, Dowling Building.

*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, MAY 8

*9:00–10:00 a.m. Medical clinic. Dr. Samuel Proger. Joseph H. Pratt Diagnostic Hospital.

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, MAY 9

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, MAY 10

*9:00–10:00 a.m. Electric Shock Treatment. Dr. Abraham Myerson. Joseph H. Pratt Diagnostic Hospital. New England Oto-Laryngological Society. Spring meeting. Massachusetts Eye and Ear Infirmary.

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

APRIL 29. Long Island College of Medicine. Page ix, issue of March 30.

MAY 3–26. Joseph H. Pratt Diagnostic Hospital. Medical Conference program. Notice elsewhere on this page.

MAY 8–14. War Conference on Industrial Medicine, Hygiene and Nursing. Page x, issue of March 23.

MAY 11. Problems of the Department of Industrial Accidents. Mrs. Emma S. Tousant. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

MAY 12. Washingtonian Hospital. Lecture on Alcoholism. Notice elsewhere on this page.

MAY 23 and 24. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

JUNE 7–13. American Board of Obstetrics and Gynecology. Page x, issue of March 23.

JUNE 8–10. American Board of Internal Medicine. Page x, issue of April 20.

JUNE 12–16. American Medical Association. Page 798, issue of November 18.

JUNE 12–16. American Physicians' Art Association. Page x, issue of March 2.

OCTOBER 3–5. American Public Health Association. Page ix, issue of March 30.

DISTRICT MEDICAL SOCIETIES

SUFFOLK

MAY 4. Censors' Meeting. Page xiii, issue of February 10.

WORCESTER

MAY 10. Annual meeting.